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Enantioselective Syntheses of 2,3-Dihydro-*4H*-pyran-4-ones and 3(*2H*)-Furanones

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Abstract

This thesis concerns the construction of 2,3-dihydro-*4H*-pyran-4-one and 3(*2H*)-furanone ring systems by mercury(II)-catalysed reactions, or by more conventional cyclisations, and the potential of such reactions for the synthesis of natural products.

Chapter one provides a literature survey of reactions permitting the construction of 2,3-dihydro-*4H*-pyran-4-one and 3(*2H*)-furanone ring systems; background literature to relevant natural products is also provided, such as polyether antibiotics, carbohydrates and antitumer agents.

Chapter two describes the application of mercury(II)-catalysed cyclisations of dihydroxylated ynones to give 3(*2H*)-furanones; this was achieved by the dihydroxylation of enynones using Sharpless's asymmetric dihydroxylation conditions followed by treatment with a mecury(II) catalyst. The scope and limitations of this method were investigated and shown in several cases to give good yields and high enantiomeric excess. In cases where there was an electron-donating group on the alkyne functionality, such as an ethoxy group, the cyclisation occurred spontaneously during the dihydroxylation step. This methodology was applied for the synthesis of a natural product to confirm the selectivity of the cyclisation step.

In *chapter three* the reactions developed in chapter two formed the basis of a proposed route to the natural product (-)-Pestalotin, a gibberellins synergist. Thus, the Sharpless asymmetric dihydroxylation method was applied to β,γ-unsaturated ketones to give a main intermediate for the synthesis.

Chapter four details different approaches to NK10958P, a plant growth regulator. The synthesis of two main fragments was achieved and the coupling of these fragments by syn-selective aldol addition is expected to furnish NK10958 P and its methyl analogue, pironetin, which has been reported to have good cytotoxic and immunosuppressive activity.

Full experimental details follow chapter 2-4 and reference sections are provided at the end of each chapter

Acknowledgement

I have greatly appreciated advice, support and comments from many people and I am particularly grateful to my academic supervisor Professor Charles M. Marson, and Dr Dave T. Davis my industrial supervisor (GSK), who made helpful suggestions throughout the duration of my Ph.D. Also I would like to thank the EPSRC and GSK for financial support for this work.

Finally I would like to thank the following people for their kind help and support; Dr A. E. Aliev, David Butler and John Hill, as well as the CMM group past and present, in particular Dr Stéphane Sengmany, and James Morrell.

Abbreviations

AD	Asymmetric Dihydroxylation
AIBN	Azoisobutyronitrile
BMS	Borane-methylsulphide complex
BINAP	2,2'-*Bis*(diphenylphosphino)-1,1'-binapthyl
Bn	Benzyl
*m*CPBA	*meta*-Chloroperoxybenzoic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DHQD	Dihydroquinidine
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodate
DMS	Dimethylsulphide
DMSO	Dimethylsulphoxide
Im	Imidazole
Ipc	Isopinocampheyl
KHMDS	Potassium bis(trimethylsilyl)amide
K-Selectride	Potassium *tri-sec*-butylborohydride
LDA	Lithium diisopropylamide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-oxide
PCC	Pyridinium chlorochromate
Ph	Phenyl
p-TsOH	*p*-Toluenesulphonic acid
Py	Pyridine
Red-Al	Sodium *bis*(2-methoxyethoxy) aluminium hydride
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride

Contents

Chapter 1

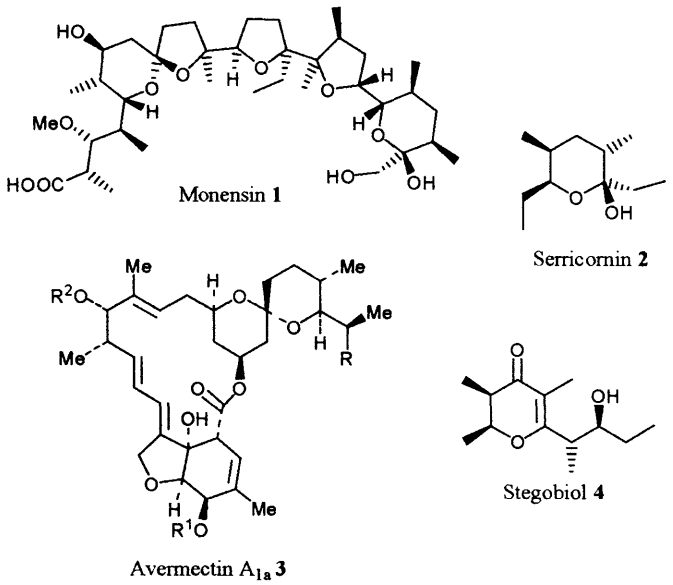
Syntheses of 2,3-Dihydro-*4H*-pyran-4-ones and 3(*2H*)-Furanones

The dihydropyranone ring system is present in a variety of natural products with important therapeutic properties. Dihydropyranones have also been used as key intermediates in the synthesis of other ring systems, such as spiroketals and substituted tetrahydropyrans.

Tetrahydropyran ring systems are part of the backbone of various carbohydrates and are important building blocks in many biologically active natural products such as marine toxins and polyether antibiotics.[1,2] Due to the synthetic interest in this ring system a number of methods have been developed for the construction of pyran rings. These include manipulation of carbohydrates,[3] Prins reactions,[4,5] hetero Diels-Alder cyclisations,[6] intramolecular epoxide opening and Michael reactions.[7]

1.1 Natural Products Containing the Dihydropyranone Ring and Related Systems

The 3-methyltetrahydropyran unit is present in the spiroketal antibiotics oligomycin, rutamycin and cytovaricin which are specific inhibitors of mitochondrial ATPase.[8] Other examples of compounds containing a 3-methyltetrahydropyran unit include monensin **1**,[9,10] a member of the polyether antibiotics (ionophores), the potent antitumour agent spongistatin[11,12] and serricornin **2**,[13] the sex pheromone of the cigarette beetle, as well as mycalamides,[14] potent antitumour and antiviral agents. The syntheses of avermectins **3**,[15] phyllanthostatins[16] and milbemycins[17,18] require assembly of a spiroketal unit, see Figure 1.1.



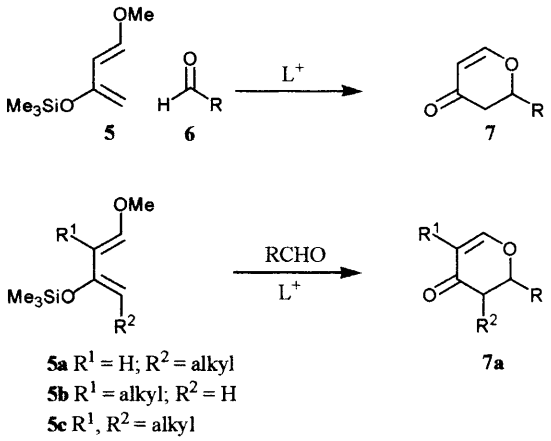
R = Et, R^1 = Me, R^2 = L-oleandrosyl-L-oleandrose

Figure 1.1: Tetrahydropyran and spiroketal-containing natural products.

The 2,3-dihydro-*4H*-pyran-4-one ring is also present in a number of natural products including stegobiol **4**,[19] a component of the sex pheromone produced by females of the drugstore beetle, vallartanones A, B[20] and various HIV protease inhibitors.[21-23]

1.2 The Total Synthesis of Dihydropyranones

Dihydropyranones are important intermediates for the synthesis of a wide range of substituted tetrahydropyrans. The synthesis of these systems is usually achieved using Lewis-acid catalysed reactions of siloxydienes **5** and aldehydes as developed by Danishefsky.[24] This reaction has been successfully used for the synthesis of polypropionate[25] and carbohydrate units, the latter being present in a variety of antibiotics[26] and antitumour agents.[27] The enantioselective syntheses of dihydropyranones **7** have been reported using chiral aldehydes,[28,29] chiral auxiliaries[30,31] attached to the diene and chiral Lewis acids.[30-32]



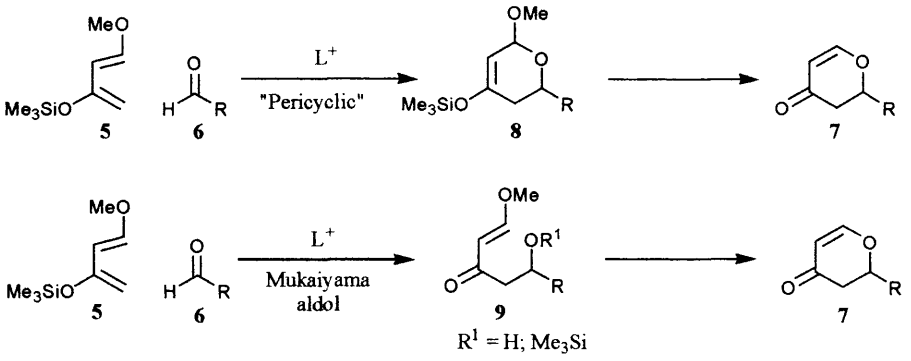
Scheme 1.1: Dihydropyranone synthesis using the Danishefsky reaction.

1.2.1 The Synthesis of Dihydropyranones Using Danishefsky's Diene

Enol silylation provides convenient access to extensively functionalized 1,3-butadienes of type **5**. It was found that under Lewis-acid catalysis the parent diene **5** reacts with a number of aldehydes to provide 2-substituted 2,3-dihydro-γ-pyrones of the general structure **7** (Scheme 1.1).[33]

In the initial experiments, zinc chloride in tetrahydrofuran or borontrifluoride etherate in dichloromethane was used as catalyst. Subsequently dienes of type **5a-c** were shown to undergo the cyclocondensation reaction. New catalytic systems were applied to the transformation, including $Eu(fod)_3$,[24] $TiCl_4$, and $MgBr_2$.

The synthesis of the dihydropyranone ring is believed to occur by one of two possible pathways, a pericyclic or an aldol-type pathway[28] (Scheme 1.2).



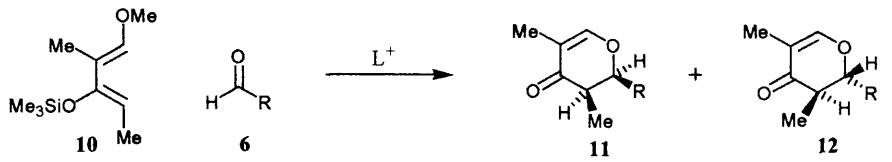
Scheme 1.2: Preparation of dihydropyranones using Danishefsky's diene **5**.

The pericyclic mechanistic model proposes a cyclocondensation reaction analogous to the catalysed all-carbon hetero Diels-Alder (HDA) reaction and favours a topology leading to the *cis*-2,3-dihydopyran. The alternative mechanism proposed involves the formation of an intermediate β–alkoxy enone **9** by a Mukaiyama variant of the aldol condensation reaction followed by ring-closure to give **7**. The reaction mechanism is greatly affected by the choice of catalyst, solvent system and the structure of the aldehyde.

1.2.2 The Diastereocontrol of the Danishefsky Reaction

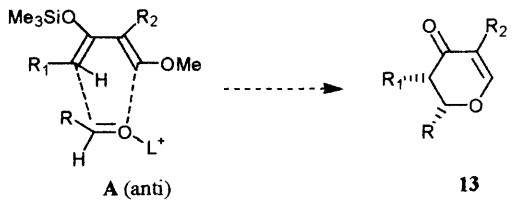
The diastereofacial control is dependent on a number of factors such as the substrate, solvent and catalyst. It was found that the borontrifluoride etherate catalyst in dichloromethane is a *trans* (threo) selective system (See Table 1.1, method A), while the zinc chloride/ tetrahydrofuran system promotes *cis* (erythro) selectivity (method B).[34] This enabled some control of the stereochemical outcome of the cyclocondensation reaction by simply changing the catalyst/ solvent system.

Table 1.1: Lewis-acid catalysed cyclocondensation reaction.



R	Method	**11** (Yield %)	**12** (Yield %)
a $^{n}C_5H_{11}$	A [(i) BF_3-CH_2Cl_2, -78 °C; (ii) TFA]	21	69
	B [(i) $ZnCl_2$-THF; (ii) $NaHCO_3$; (iii) TFA]	91	2
b C_6H_5	A	23	68
	B	78	2
c $C_6H_5(CH_2)_3$	A	17	64
	B	83	2
d $C_6H_5CH_2OCH_2$	A	17	68
	B	66	24

The formation of the *cis* products (Scheme 1.3) corresponds to an *endo* orientation of the R group of the aldehyde relative to the diene. This mechanism can be explained in terms of the formation of a complex where the Lewis acid (L^+) binds to the aldehydic oxygen anti to the R group. Thus steric factors might favour positioning the Lewis acid in the *exo* orientation in the pericyclic process, thus resulting in the *cis*-pyranone **13**.



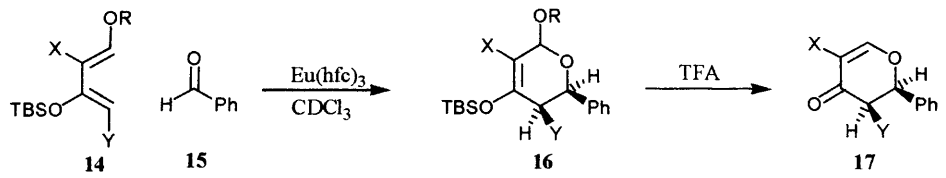
Scheme 1.3: Diastereocontrol of the Danishefsky reaction.

1.2.3 Enantioselectivity of the Danishefsky Reaction

Some enantioselectivity was achieved by using chiral aldehydes; however, this approach is limited by the availability of the chiral aldehyde and the level of success in the transmission of the stereochemical information from the chiral aldehyde to the emerging dihydropyran.

With achiral dienes, the commercially available chiral catalyst $Eu(hfc)_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium] shows only modest enantiofacial selectivity (Table 1.2); similarly, modest enantioselectivities were observed in the reactions of several chiral dienes and aldehydes in the presence of the achiral catalyst $Eu(fod)_3$ (Table 1.3). However, the combination of chiral dienes with chiral $Eu(hfc)_3$ catalyst exhibited remarkable interactivities, which led in some instances to diastereofacial excesses of 95% (Table 1.4).[30]

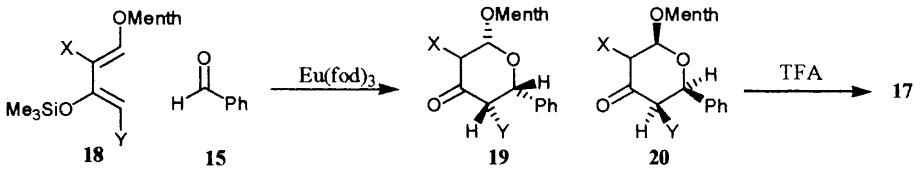
Table 1.2: Ratio of *L*-Dihydropyrone **17**/ *D*-Dihydropyrone ent-**17** for the Reaction of Dienes **5** with Benzaldehyde. (Catalyst, (+)-$Eu(hfc)_3$; solvent, $CDCl_3$ (R = *tert*-butyl).



14 **15** **16** **17**

Compound	X	Y	**17**/ ent-**17**
(a)	H	H	69/31
(b)	Me	H	70/30
(c)	Me	Me	71/29
(d)	OAc	H	66/32
(e)	$OSiMe_3$	H	71/29

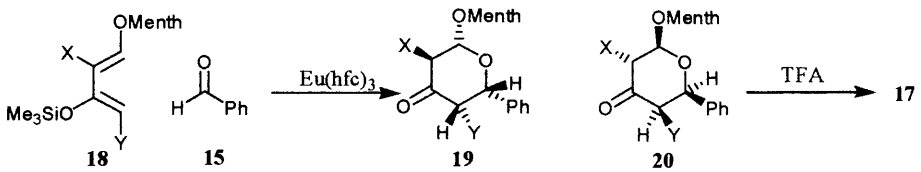
Table 1.3: Ratios of *D*-Pyranose **19**/ *L*-Pyranose **20** for the Reaction of *l*-Menthyloxy Dienes **18a-d** with Benzaldehyde. (Catalyst, $Eu(fod)_3$; solvent, $CDCl_3$).



Compound	X	Y	**19/ 20**
(a)	H	H	33/67
(b)	Me	H	45/55
(c)	OAc	H	45/55
(d)	Me	Me	49/51

A study of the efficacy of combining the chiral catalyst $Eu(hfc)_3$ with the chiral dienes **18** showed that the use of modestly *L*-selective diene in conjunction with the modestly *L*-selective (+)-$Eu(hfc)_3$ catalyst resulted in poor selectivity for *L*-pyranone. However, the combination of (-)-$Eu(hfc)_3$ with the modestly *L*-selective diene provided substantial diastereotopic preferences for L-pyranose **19**/ D-pyranose **20**.[35] The results are given in Table 1.4.

Table 1.4: Ratios of *D*- and *L*-Pyranosides for the Reaction of Menthyloxy Dienes **18a-d** with Bezaldehyde. Catalyst, $Eu(hfc)_3$; solvent, $CDCl_3$.



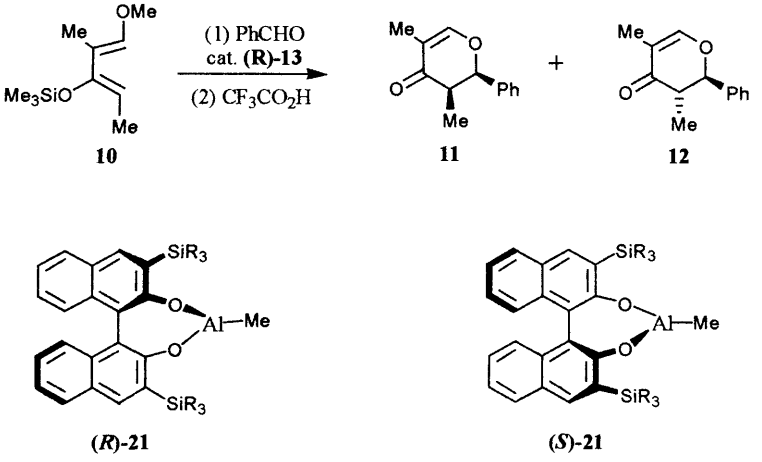
Compound	X	Y	**19/ 20**
(a)	H	H	75/25
(b)	Me	H	92/8
(c)	OAc	H	93/7
(d)	Me	Me	87/13

As a result of *endo* selectivity, only *cis* pyranones are directly available through this methodology. Additionally, this reaction does not allow the direct synthesis of aryl or alkyl C-6 substituted dihydropyranones.

Another limitation is for unsubstituted dienes, where X,Y=H (Danishefsky's Diene) which function well in the cycloaddition reaction, but afford poor diastereoselectivity even in the presence of different chiral auxiliaries with either of the $Eu(hfc)_3$ antipodes or in the presence of the achiral $Eu(fod)_3$ as the catalyst.

1.2.4 Further Modifications to the Danishefsky Reaction

Yamamoto and co-workers described the successful application of organoaluminium catalysts ((*R*)-**21** / (*S*)-**21**) to affect the Danishefsky reaction (Scheme 1.4), leading primarily to the *cis*-substituted product (*cis*: *trans* 77:7) in 84% yield and 95% ee.[32] The enantioselectiviy was established by the presence of bulky aryl groups (R = Ph or 3,5-xylyl) on the silyl group of the catalyst.



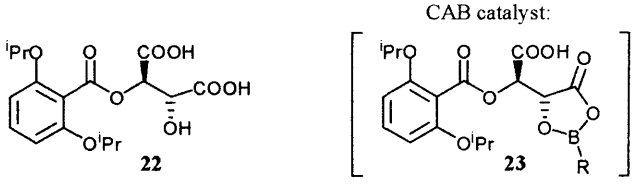
Scheme 1.4: Enantioselective synthesis of dihydropyranones by the Danishefsky reaction using an organoaluminium catalyst (R = Ph or 3,5-xylyl).

The optical purity of the product was independent of the amount of catalyst used (5-100 mol%), but it increased gradually by lowering the reaction temperature. The choice of the bulky triarylsilyl moiety in **21** is crucial for obtaining the high enantiofacial selectivity. The reaction of benzaldehyde with the diene **10** in the

presence of catalyst (***R*)-21** (Ar = Ph), its *tert*-butyldimethylsilyl analogue and its trimethylsilyl analogue under similar conditions produced **11** and **12** respectively in yields of 84% (ratio, 92:8, 95% ee in **11**), 91% (69:31, 84% ee), and 72% (53:47, 64% ee). Since both enantiomers of the catalyst are available both antipodal products can be obtained via this route. In the case of benzaldehyde, the enantioselective activation of the carbonyl moiety by the catalyst positions the diene in an *endo* alignment relative to the aldehyde phenyl residue, which minimizes steric repulsion between the incoming diene and the front triarylsilyl moiety, thereby yielding the *cis* adduct **11**, see Scheme 1.4.

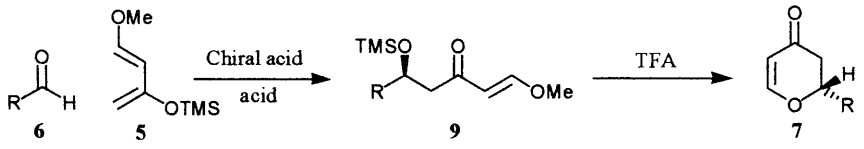
Once the hetero-Diels-Alder adduct is formed the aluminium reagent is cleaved and the catalyst is available for further use in the catalytic cycle. In contrast, the chiral organoaluminium reagents derived from Me_3Al and (*R*)-(+)-3,3'-dialkylbinaphthol (alkyl = H, Me, and Ph) was employable only as a stoichiometric reagent and gave fewer satisfactory results in reactivity and enantioselectivity of the dihydropyranone product.

A solution of the chiral (acyloxy)borane (CAB) catalyst, prepared by the reaction of tartaric acid derivative **22** and arylboric acid was reported to affect the hetero Diels-Alder reaction.[36] The cyclocondensation was carried out with 20 mol% of the CAB catalyst at -78 °C. Treatment of the crude product with trifluoroacetic acid in dichloromethane afforded the dihydropyranone product. The extent of asymmetric induction was largely dependent on the structure of boric acid; where R = Bu or Ph the ee of the dihydropyrone was 73% (63% yield), whereas bulky phenylboric acid (2,4,6-Me_3Ph) resulted in an excellent ee of 95% (47% yield), overly bulky substituents, however, led to a loss in reactivity.



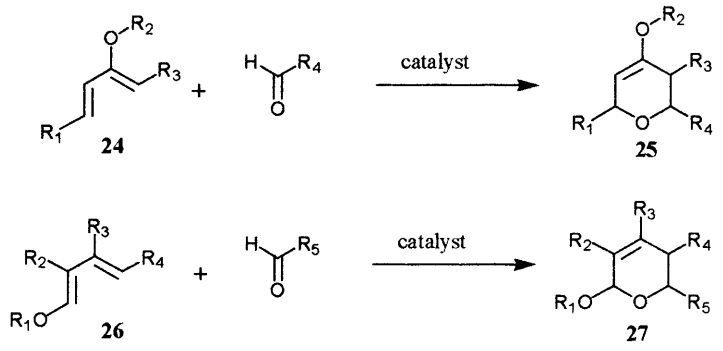
Scheme 1.5: CAB catalyst and tartaric acid precursor.

The catalytic enantioselective aldol reaction was reported by Keck and co-workers, using $Ti(O^iPr)_4$/ BINOL (*R*- or *S*- enantiomer) catalyst.[37] This reaction was followed by trifluoroacetic acid-catalysed cyclisation to furnish the dihydropyranone **7** (Scheme 1.6). The cyclocondensation reaction between various simple aldehydes and 1-methoxy-3-[(trimethylsilyl)oxy]-butadiene (Danishefsky's diene) was investigated and it was reported that this procedure led to high ees (78-97%) and moderate yields.



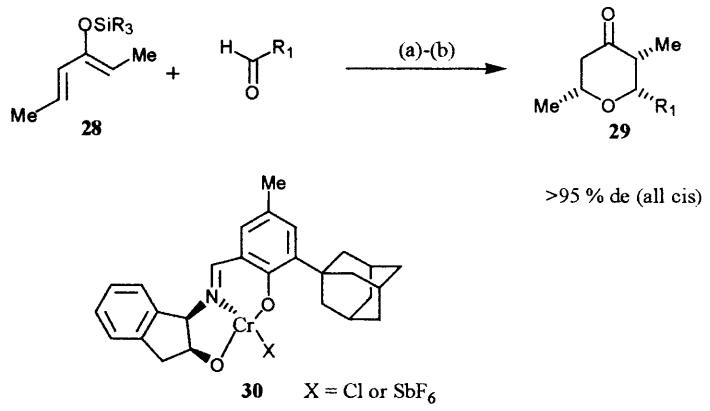
Scheme 1.6: The synthesis of dihdropyranones using the aldol reaction followed by acid-catalysed cyclisation.

The hetero Diels-Alder reaction reported by the Danishefsky group usually involved electron-rich dienes such as 1-methoxy-3-(trimethylsilyloxy) butadiene (Danishefsky's Diene) and/or electron-deficient dienophiles such as glyoxylates derivatives. Recently Jacobsen and co-workers reported the asymmetric hetero Diels-Alder reaction between less nucleophilic dienes, such as **24** or **26** and unactivated carbonyl compounds using the tridentate Schiff base chromium(III) complexes **30** (Schemes 1.7 and 1.8).[38]



Scheme 1.7: The chromium(III) catalysed cyclisation of electron-deficient substrates.

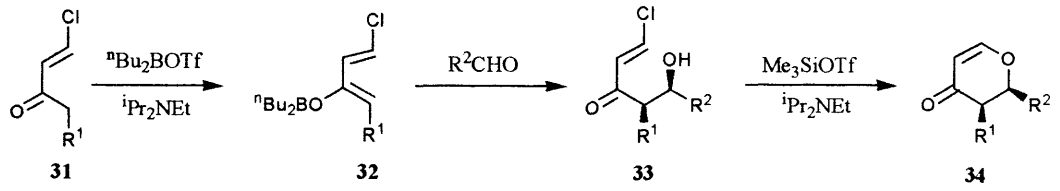
The adamantyl-substituted chromium(III) complexes **30** led to high ees (95%) and the high *endo* selectivity of the cyclisation step resulted in the formation of the mainly *cis*-configuration products. This reaction was shown to tolerate a wide range of aldehyde starting material and thus led to highly substituted 2,6-*cis*-tetrahydropyran rings.[39,40]



Scheme 1.8. *Reagents and conditions:* (a) catalyst **30** (3 mol%), 20°C, 16-40h (b) TBAF, AcOH, THF.

1.2.5 Alternative Methods for the Preparation of 2,3-Dihydropyranones

Paterson and co-workers reported the diastereoselective preparation of the *syn*-aldol product **33** (97% de in some cases) using the dienol dibutylborinates **32**.[41] The cyclisation of **33** in the presence of trimethylsilyltriflate generated the *cis*-dihydropyranone product **34** (Scheme 1.9). However, equilibration between the *cis*-dihydropyranone (kinetic product) and the *trans*-isomer, resulted in lower selectivity in some cases (*cis*:*trans* 70:30). Enantioselectivity was achieved by using the chiral boron reagent (-)-$(Ipc)_2BOTf$ for the enolisation step, which in one case resulted in the formation of the aldol product in 97% diastereoselectivity and 80% ee.



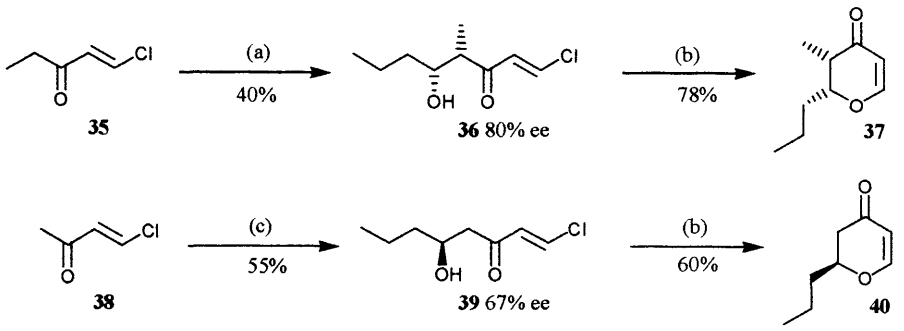
31 **32** **33** **34**

Scheme 1.9: Preparation of dihydropyranones by an aldol-cyclocondensation reaction. (R^1 = Me, R^2 = Alkyl).

For R^1 = Me, the boron-mediated aldol reaction of **31** with a range of aldehydes produced the *syn* adduct **34** in good yield (53-84%) with high *syn* selectivity (97%) via the (*Z*)-dienol dibutylborinates **32**. Selective production of the *anti* isomer *via* the corresponding (*E*)-dienol borinates, however, proved unsatisfactory. For R^1 = H, the corresponding aldol reaction of the enone **31** also proceeded well.

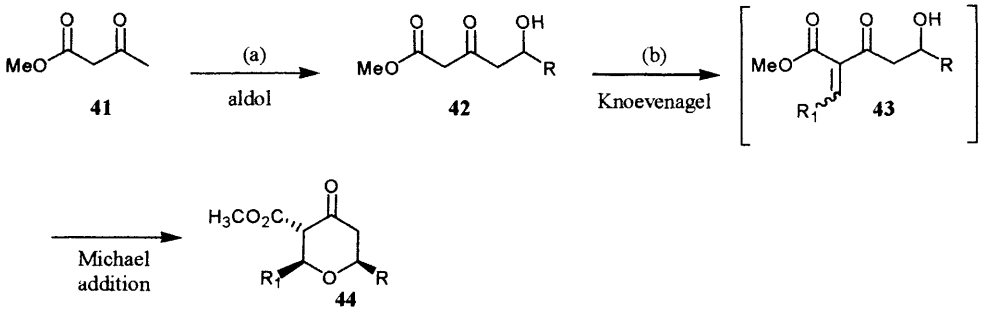
The cyclisation could not be extended to the situation where R^2 is phenyl or alkenyl as competitive dehydration occurred. It is believed that the reaction proceeded through the trimethylsilyl ether derivatives of **33**, which then undergo acid (or trimethyl silyl triflate) catalysed cyclisation to the dihydropyrone.

The asymmetric synthesis of dihydropyrones by chiral boron reagents for the initial aldol step was investgated. Use of (-)-$(Ipc)_2BOTf$ (1.3eq) for the enolisation of **35** gave the *syn*-aldol product **36** (40%, >97% diastereoselectivity) in 80% ee (determined by analysis of the ^{1}HNMR spectra in the presence of $Eu(hfc)_3$), cyclisation resulted in the *cis*-dihydropyrone **37** in 78% yield and 80% ee. Hence no detectable racemisation occurred during the cyclisation step. Similarily, the (-)-$(Ipc)_2BCl$ mediated aldol reaction of **38** with butanal gave **39** in 67% ee which was cyclised to give the dihydropyrone **40** (Scheme 1.10).



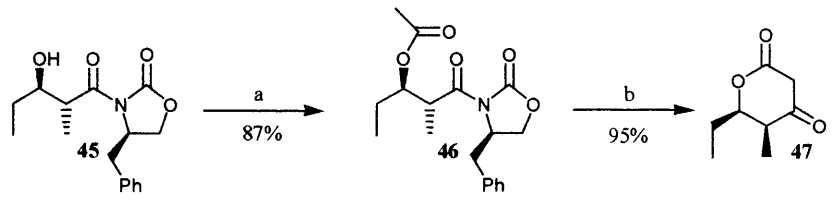
Scheme 1.10. *Reagents and conditions:* (a) (i) (-)-$(Ipc)_2BOTf$, $^iPr_2NEt$, CH_2Cl_2; (ii) ^nPrCHO; H_2O_2; (b) Me_3SiOTf, $^iPr_2NEt$; (c) (i) (-)-$(Ipc)_2BCl$, $^iPr_2NEt$, CH_2Cl_2; (ii) ^nPrCHO; H_2O_2.

Clarke and co-workers reported the synthesis of substituted tetrahydropyran-4-ones in single diastereoisomers by an aldol reaction between β-ketoesters with aldehydes followed by a tandom Knoevengel condensation with a further equivalent of aldehyde, and an intramolecular Michael addition (Scheme 1.11).[42,43]



Scheme 1.11. *Reagents and conditions:* (a) (i) NaH, THF (ii) ^nBuLi, -78 °C (iii) RCHO (b) (i) $BF_3.OEt_2$, THF (ii) R_1CHO.

A recent publication by Hinterding and co-workers described the preparation of β-keto-δ-lactone by an intramolecular Claisen-type rearrangement on Evans oxazolidinone with an acetate enolate[44] (Scheme 1.12); the anti-aldol **45** was initially converted to the acetate **46** by treatment with acetic anhydride in the presence of triethylamine and DMAP. The exposure of compound **46** to a solution of LiHMDS (lithium-bistrimethylsilylamide) led to the clean formation of the lactone product **47** with the chiral oxazolidinone being generated as the only by-product.



Scheme 1.12. *Reagents and conditions*: (a) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 20°C; (b) LiHMDS, THF, – 78°C.

1.2.6 Cyclisation of Hydroxy Alkynones to 2,3-Dihydropyranones

1.2.6.1 Baldwin's Rules for Ring Closure

Baldwin has proposed a set of rules for ring closure;[45] the ring-forming reactions are designated by a numerical prefix which denotes the ring size, which is then followed by either the term *exo* or *endo* depending on whether the bond breaking is exocyclic or endocyclic to the smallest ring formed, and finally by one of the suffixes *tet*, *trig* or *dig* describing the hybridisation of the carbon atom undergoing attack in the cyclisation step, referred to as *tetrahedral*, *trigonal* and *digonal* respectively. Scheme 1.13 illustrates some of the different possibilities of ring closure for the digonal case.

The rules are as follows:-

Rule 1: Tetrahedral Systems:

(a) 3 to 7-*Exo-Tet* are all favoured processes with many reported in the literature.

(b) 5 to 6-*Endo-Tet* are disfavoured.

Rule 2: Trigonal Systems:

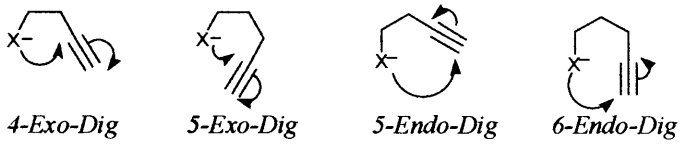
(a) 3 to 7-*Exo-Trig* are all favoured processes with many literature precedents.

(b) 3 to 5-*Endo-Trig* are disfavoured; 6 to 7-*Endo-Trig* are favoured.

Rule 3: Digonal Systems:

(a) 3 to 4-*Exo-Dig* are disfavoured processes; 5 to 7-*Exo-Dig* are favoured.

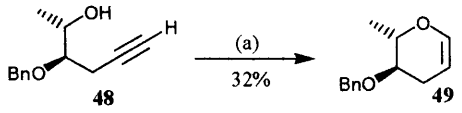
(b) 3 to 7–*Endo-Dig* are favoured.



Scheme 1.13: Digonal cyclisations.

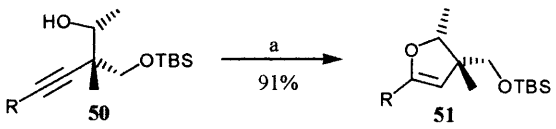
1.2.7 Preparation of Dihydropyranones Using β-Hydroxy Alkynes

A series of molybdenium and tungsten-mediated cycloisomerisation of homopropargylic and bis-homopropargylic alcohols to dihydrofurans and dihydropyrans has been reported by McDonald and co-workers (Scheme 1.14).[46,47] However, this requires photolysis at elevated temperatures as well as high catalyst loading (25%).



Scheme 1.14. *Reagents and conditions*: (a) (i) $(THF)W(CO)_5$, THF; (ii) NEt_3, Et_2O/THF.

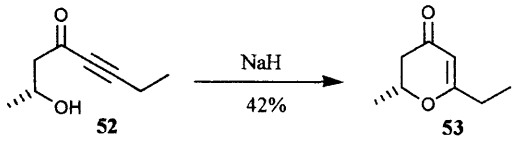
Simillarily, palladium(II) catalysts have been used to affect the cyclisation of propargylic alcohol **50** into the dihydrofuran **51** in excellent yields (Scheme 1.15).[48]



Scheme 1.15. *Reagents and conditions*: (a) $PdCl_2(PhCN)_2$, MeCN, 60°C.

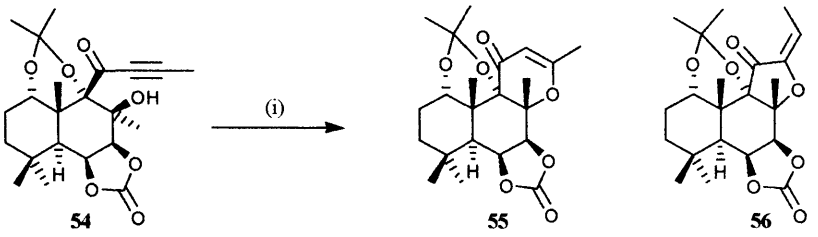
The cyclisation of β-hydroxy alkynones **52** to form dihydropyranone **53** in the presence of NaH was observed by Dreessen and co-workers.[49] The reaction occurs by an intramolecular conjugate addition of the hydroxyl group to the ynone.[50,51] This

cyclisation was also effected using a solution of TBAF in THF at 20 °C, and resulted in a 43% yield of the dihydropyranone.[52]



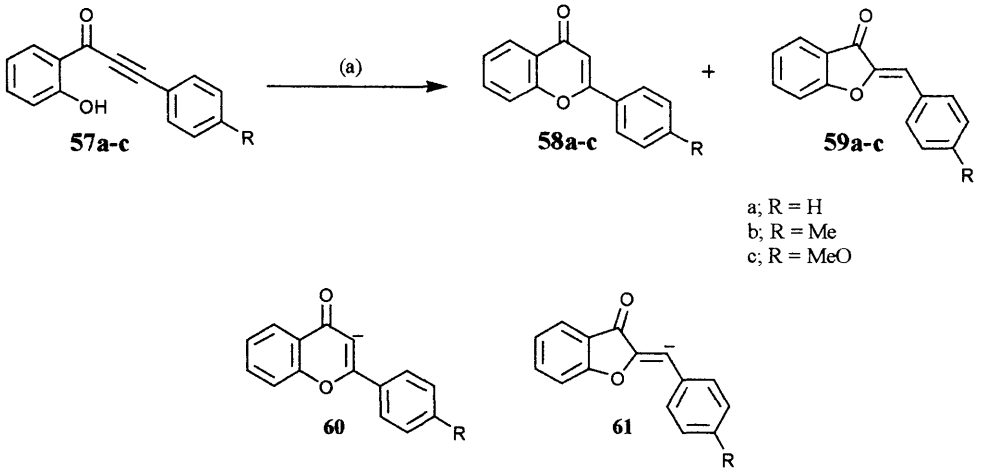
Scheme 1.16: Base-catalysed synthesis of dihydropyranones.

Ziegler and co-workers obtained poor yields of the dihydropyranone **55** (30-49%) by using caesium carbonate as a catalyst in acetonitrile. The poor yield was a consequence of the formation of the 5-*exo-dig* product **56** (39-50%),[53] (Scheme 1.17).



Scheme 1.17: Preparation of dihydropyranone **55** from β–hydroxy alkynone **54**, (i) Cs_2CO_3, MeCN, 20 °C, 15-21%.

The cyclisation of **57a-c** under basic conditions resulted in a mixture of flavones **58a-c** and aurones **59a-c** products *via* 6-*endo-dig* and 5-*exo-dig* modes of cyclisation respectively (Scheme 1.18); the product distribution is dependent on the nature of the alkyne substituent (R). The cyclisations are presumed to occur via the respective vinylic carbanion precursors **60** and **61**. The more inductively electron-donating the β-phenyl ring the less stable the carbanion **61**, and hence less aurone is seen in the product mixture, see Table 1.5.



Scheme 1.18. Base-catalysed cyclisation of 1-(2-hydroxyphenyl)-3-arylprop-2-yn-1-ones. *Reagents and conditions:* (a) NaOMe (1.1 eq.), MeOH, 20°C, 2 h.

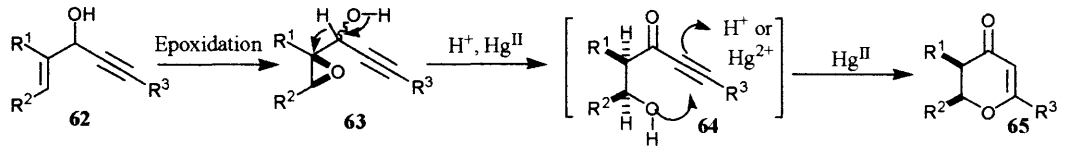
Table 1.5: Product distribution for NaOMe-catalysed cyclisation in MeOH.

Compound	Yield (%)	Flavone **58** (%)	Aurone **59** (%)
57a	86	59	41
57b	91	70	30
57c	95	74	26

The cyclisation was also carried out in the presence of trifluoroacetic acid (TFA), under these conditions electron-donating substituents (R) caused the reaction to proceed more rapidly and the flavone product was favoured, (*i.e.* the 6-*endo-dig* cyclisation product); the reaction was performed at 20 °C or at reflux for 24-48 hours.

1.2.8 Synthesis of 2, 3-Dihydropyranones Using Mercury(II)-Catalysed Rearrangement of Epoxy Alkynols

Marson and co-workers reported the first examples of 1-alkynyl-2,3-epoxy alcohol rearrangement leading to 3-substituted-2,3-dihydro-*4H*-pyranones (Scheme 1.19).[54] The reaction is believed to occur via a semi-pinacol rearrangement of the epoxide, followed by ring-closure. However, the intermediate **64** has not been isolated and so an alternative pathway may be operating.

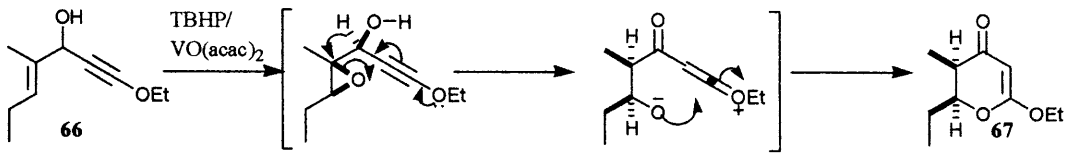


Scheme 1.19: Stereospecific rearrangement of epoxy alkynols to 2,3-dihydro-*4H*-pyran-4-ones.

It was concluded that the configuration of the alkene (that is epoxidized) exclusively determines the configuration of the resulting 2,3-disubstituted dihydropyran; thus a *trans*-(*E*)-alkene would lead solely to the dihydropyranone **65**, with *cis* 2,3-substitution, the (*Z*)-alkene affords the *trans*-product. This was explained by the suprafacial migration of hydride, with concomitant ring opening of the epoxide, and inversion solely at the α-position. Where needed, asymmetric epoxidation can be used to provide enantioselective syntheses of dihydopyranones and related natural products, such as those discussed in section 1.1.

The 2,3-epoxy alcohols **63** were prepared from enynols **62** using *tert*-butyl hydroperoxide (TBHP)-$VO(acac)_2$ with the subsequent cyclisation being catalysed by mercury(II) in dilute aqueous sulfuric acid. The configuration of the carbinol carbon atom was considered to be unimportant as free rotation will enable both the epimeric alcohols to deliver the hydride *anti* to the C-O bond of the epoxide undergoing cleavage.

The mild reaction conditions enabled the tolerance of alkyl, aryl and hydroxylated functionalities at the C6 position of the ring as long as the group is not substantially electron-withdrawing. It was also found that placement of an electron-donating group, *e.g.* ethoxy, at C-6 led directly to the 2,3-dihydropyranone **67** from the allylic alcohol during the epoxidation step, as no epoxide was isolated the mercury catalyst was not required in this case (Scheme 1.20).



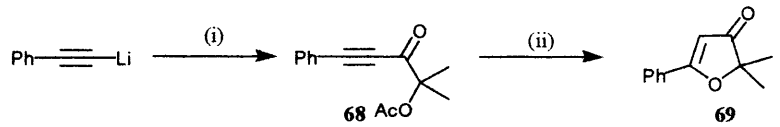
Scheme 1.20: Proposed pathway for tandem epoxidation-cyclisation.

As the ethoxy group is a strong electron donor, the movement of electrons shown in Scheme 1.20 may result in assisted cleavage of the epoxide ring and perhaps also to the ring closure by attack of oxygen on the "ketene oxonium" group leading to the pyranone molecule. This is a significant result, not only due to rapid formation of the pyranone but as the 6-ethoxy pyranone ring can be converted into a lactone ring in the presence of an acid, the lactone ring being common in natural products.

The above epoxidation-cyclisation route can only be applied to the synthesis of 3-substituted pyranone rings, as the cyclisation step was unsuccessful for C-3 unsubstituted epoxides. Thus a different method of synthesis is needed to obtain the 3-unsubstituted pyranone ring; one proposed method is the synthesis of β-hydroxy alkynone **64** (*e.g.* by Evans auxiliary protocol) followed by the mercury-catalysed cyclisation.

1.2.9 Preparation of 3(2H)-Furanones From α-Hydroxy Alkynones

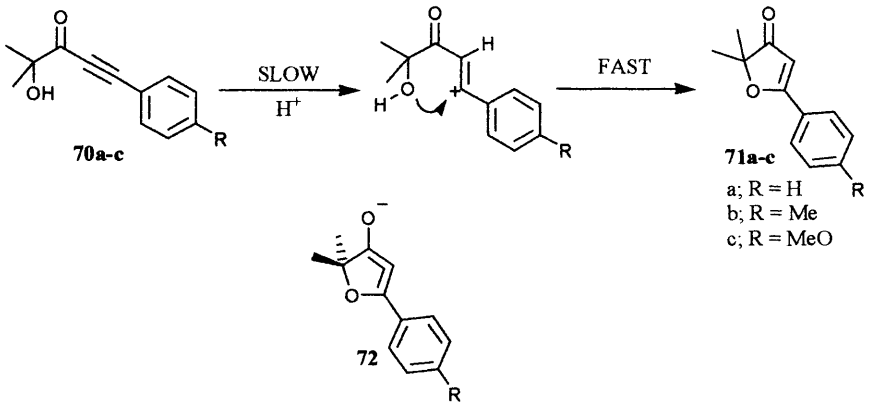
The 3(*2H*)-furanone ring system is an important synthetic target, as it is present in a number of biologically-active natural products such as bullatenone **69** and the antitumour agent geiparvarin. Jackson and Raphael[55] reported the synthesis of 3(*2H*)-furanone **69** from ynone **68** by heating under reflux in a suspension of potassium carbonate in methanol. The acetylenic ketone **68** was obtained by addition of lithium phenylacetylide to α-acetoxyisobutyryl chloride in tetrahydrofuran at – 70 °C.



Scheme 1.21: Preparation of a 3(*2H*)-furanone; (i) α-acetoxyisobutyryl chloride, THF, - 70 °C, (ii) K_2CO_3, MeOH, 35% overall yield from phenylacetylene.

According to stereoelectronic principles[56] the first intermediate of a base-catalysed addition to a conjugated acetylenic ketone (ynone) should be an allenic enolate, such as **72**, followed by protonation leading to the α,β–unsaturated ketone (enone). Also the acid-catalysed Michael-addition mechanism would proceed through an allenic enol intermediate. However, this mechanism does not account for the synthesis of rings smaller than 8-membered where the allene functionality would result in considerable ring strain.

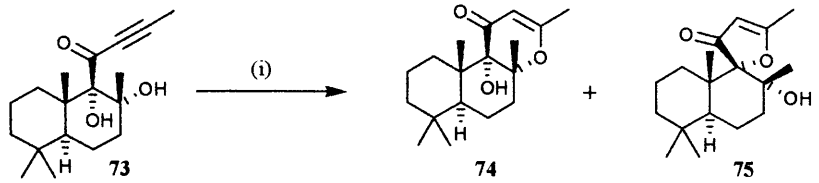
An alternative mechanism was proposed by Brennan and co-workers,[57] outlined in Scheme 1.22. It was suggested that under acidic conditions the cyclisation of ynones **70a-c** occurred by a rate-limiting protonation of the triple bond; this is followed by bending of the vinyl carbenium ion, allowing the overlap of the oxygen lone pair of the nucleophile and the vacant sp^2 orbital.



Scheme 1.22: Ring-closure reaction pathway for 2-hydroxy-2-methyl-5-arylpent-4-yn-3-ones.

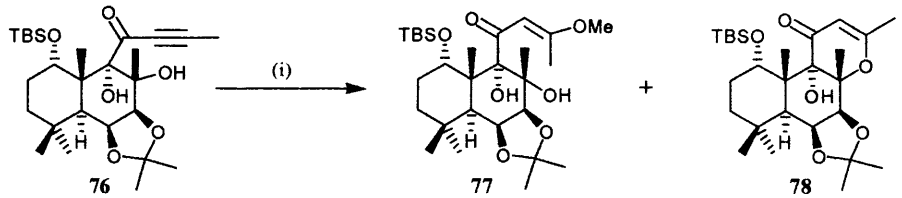
1.2.10 Cyclisation of α,β-Dihydroxy Alkynones

The treatment of the diol **73** with $Hg(OCOCF_3)_2$ using Schwartz's conditions[58] led in a regioselective manner to the dihydropyran-4-one **74** in 71% yield along with 7% of the dihydrofuran-3-one **75** (Scheme 1.23).[32;59;60]



Scheme 1.23: Dihydropyran-4-one synthesis using mercury(II) trifluoroacetate as the catalyst. (i) $Hg(OCOCF_3)_2$, Et_3N, CH_2Cl_2, - 78 °C; then LiI, Et_2O, Et_3N.

Treatment of acetylenic ketone **76** with methanolic potassium methoxide (0.03 M, 25 °C, 6 h) produced a mixture of the dihydropyranone **78** in 44% yield and the (*E*)-vinylogous ester **77** (34% yield),[61] which proved to be stable to the reaction conditions. The penultimate precursor of the dihydropyanone was assumed to be the (*Z*)-isomer of **77**. However, acid-catalysed cyclisation (*p*-TsOH, benzene, 25 °C, 5 h) of the (*E*)-isomer **77** provided the desired dihydropyranone **78** in 97% conversion (total of 76% yield from the acetylenic ketone **76**) (Scheme 1.24).

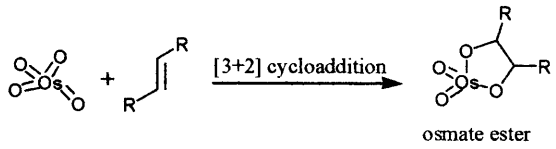


Scheme 1.24: Base-catalysed ring closure of 2,3-dihydroxyalkynones. (i) KOMe/ MeOH, 25 °C, 6 h.

When conditions (Cs_2CO_3, CH_3CN, 45 °C, 9 h) devised by Deslongchamps[56] for the intramolecular addition of β-keto ester anions to acetylenic ketones were applied to the diol **76**, exclusive formation of corresponding furanone product was observed.

1.3 Sharpless Asymmetric Dihydroxylation: Background

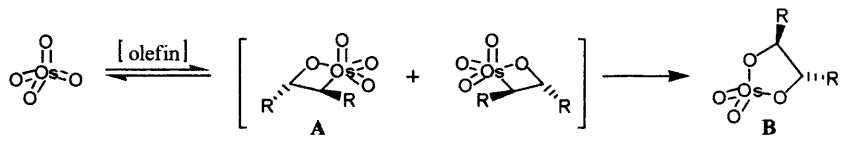
Criegee first reported the use of osmium tetroxide for the oxidation of olefins;[62] this reaction was believed to occur by a concerted [3+2 cycloaddition] mechanism (Scheme 1.25).



Scheme 1.25: Proposed [3+2] cycloaddition mechanism for the dihydroxylation of alkenes.

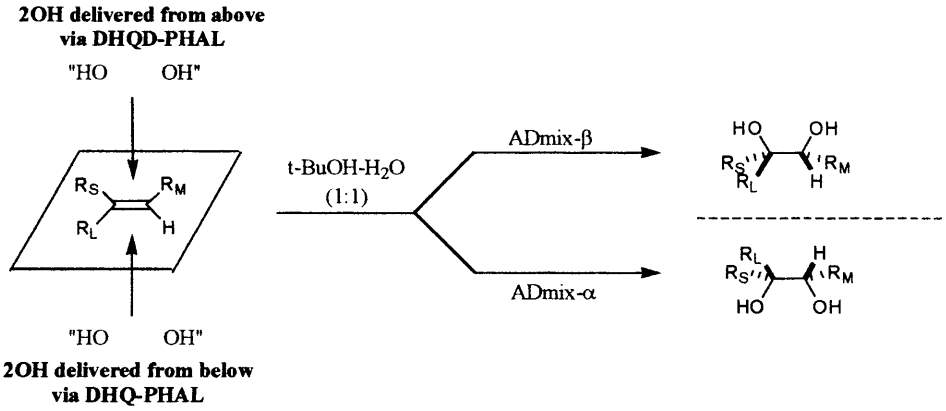
A ligand acceleration effect was reported by Criegee, originally using achiral ligands such as pyridine. Various co-oxidants were used to regenerate the osmium tetroxide catalyst with different levels of success, among those are hydrogen peroxide, N-methylmorpholine *N*-oxide (NMO) and potassium ferricyanide ($K_3Fe(CN)_6$/ K_2CO_3).

Sharpless proposed a stepwise [2+2] model for the formation of the glycol osmate ester.[63,64] In this mechanism, the olefin first coordinates to the osmium centre and this intermediate undergoes a fast and reversible rearrangement to the oxa-osmetane intermediate **A**. Bond migration then leads to the 5-membered ring osmate ester **B**, (Scheme 1.26).[65] However, balance of evidence appears to favour the [3+2] mechanism over the stepwise [2+2] pathway as the former was more consistent with the observed substrate selectivity and enantioselectivity.[66]



Scheme 1.26: Proposed [2+2] mechanism for the dihydroxylation of alkene; L symbolizes the amine or chiral alkaloid ligands.

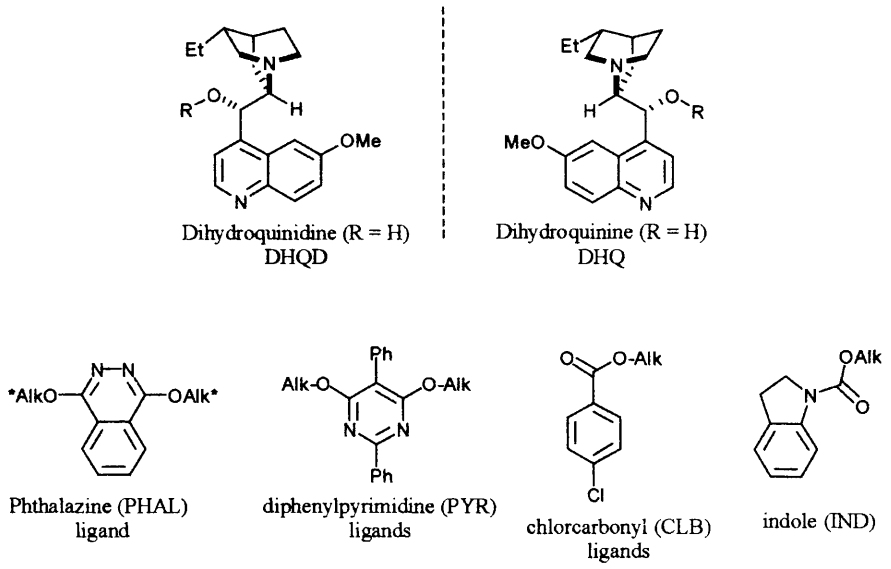
In 1988 Sharpless described the asymmetric dihydroxylation (AD) of olefins; this reaction uses osmium-based catalysts,[67] such as OsO_4 or the non-volatile osmium source $K_2[OsO_2(OH)_4]$. Other reagents involved in this reaction include the stoichiometric oxidant $K_3Fe(CN)_6$ (3 equivalents) used to regenerate the catalyst, K_2CO_3 (3 equivalents) used to control the pH of the reaction and a chiral dihydroquinine (DHQ) or dihydroquinidine (DHQD) ligand that binds to the osmium catalyst and induces the enantioselectivity of the reaction.[68] A premix of AD reagents is commercially available as ADmix-α, (containing $(DHQ)_2$-PHAL which dihydroxylates the α-face of alkenes) and ADmix-β, (containing $(DHQD)_2$-PHAL and giving the opposite enantiomer); see Scheme 1.27. Scheme 1.29 describes the catalytic cycle involved in the AD reaction.



Scheme 1.27: Sharpless Asymmetric Dihydroxylation.

1.3.1 Chiral ligands for Sharpless Asymmetric Dihydroxylation

Cinchona alkaloids, such as $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ are widely used as chiral ligands in the Sharpless AD reaction (Scheme 1.28). A series of other Cinchona alkaloid-based ligands with different linkers are applied for specific types of alkenes in order to optimise the yield and ee (Table 1.6).[67]



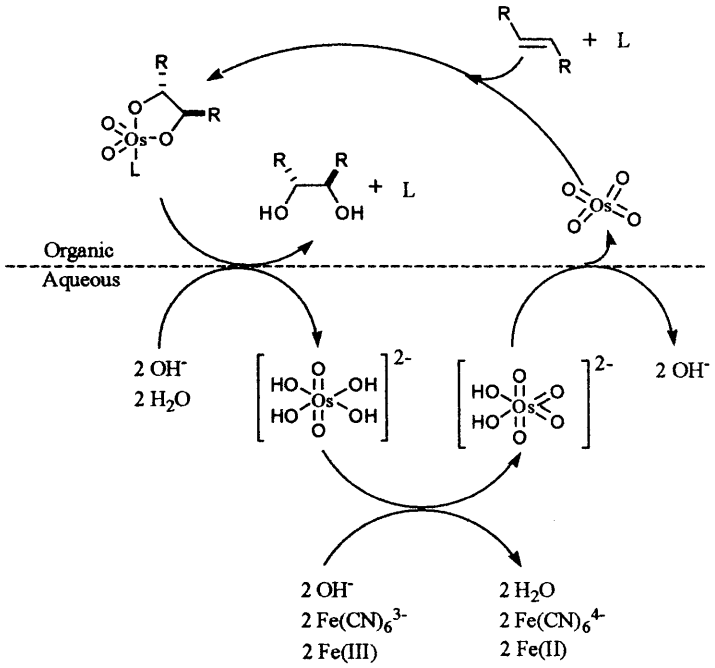
Scheme 1.28: chiral ligand library (Alk* = DHQD or DHQ).

Table 1.6: Chiral ligands used for Sharpless' AD reaction

olefin classes						
best ligand	PYR, PHAL	PHAL	IND	PHAL	PHAL	PYR, PHAL
ee range	30-97%	70-97%	20-80%	90-99.8%	90-99%	20-97%

1.3.2 Stoichiometric Co-oxidant

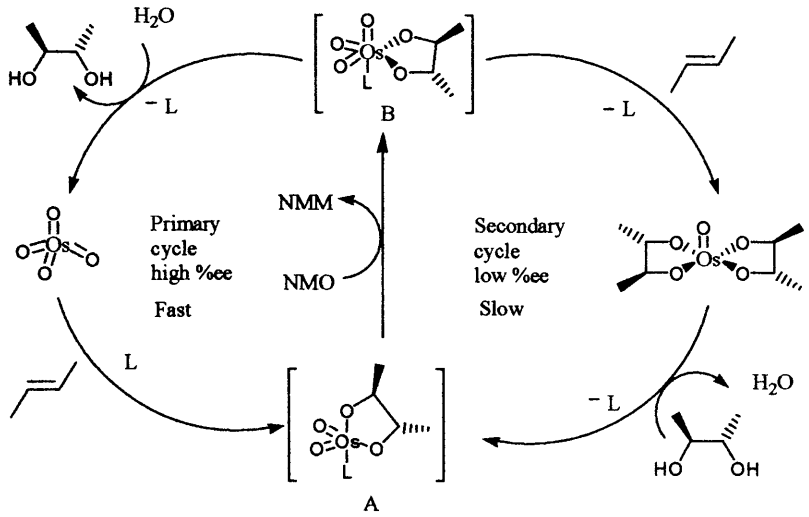
The stoichiometric co-oxidant used for the Shapless AD is potassium ferricyanide, due to its high efficiency of reoxidation of the osmium catalyst and the high ee of the resulting product (Scheme 1.29). However, a possible disadvantage is its high molecular weight, and as three equivalents are normally required it makes up most of the weight of AD-mix reagent used by this reaction (*i.e.* 1.40 g of AD-mix per mmol of the olefin substrate).



Scheme 1.29: The catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the co-oxidant.

Several oxidants such as *N*-methylmorpholine *N*-oxide (NMO), sodium peroxodisulfate ($Na_2S_2O_8$), and iodine have been used in place of ferricyanide, but proved to be much less efficient or less practicable.

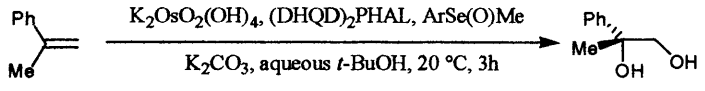
In the case of NMO, consistently high yields of the diols were obtained but it produced lower ees than those obtained using potassium ferricyanide. The lower ees observed with NMO were attributed to the presence of a second cycle of "poor selectivity", involving a trioxoglycolate complex (Scheme 1.30).



Scheme 1.30: Catalytic cycle using NMO as the co-oxidant.

Recently, selenoxides were reported to be efficient stoichiometric co-oxidants in the asymmetric dihydroxylation of olefins.[69] The reaction used the same chiral catalyst ($(DHQD)_2PHAL$, 0.016 mol equiv) and oxidant [$K_2OsO_2(OH)_4$]; potassium carbonate (0.3 equiv) was also used but only one-tenth of the amount present in AD-mix.

The dihydroxylation of α–methylstyrene (Scheme 1.31) gave the corresponding diol in yield (93%) and ee (97%) similar to those described by Sharpless using the AD-mix method.



Scheme 1.31: The application of selenoxide co-oxidants for the Sharpless AD reaction.

1.3.3 The Concentration of Osmium and Ligand

The osmium reagent usually used is OsO_4 (0.2 mol%), or as the involatile [$K_2OsO_2(OH)_4$], and 1 mol% of the ligand, i.e. PHAL or PYR. The enantioselectivity of the AD reaction has proven quite insensitive to variation in the relative amount of osmium and ligand. However, in the case of unreactive olefins the osmium

concentration may need to be increased to 1 mol% whilst maintaining the ligand concentration at the same level.

The olefin concentration is usually 0.1 M. Since the reaction is normally run under basic conditions (pH = 12.2 in the aqueous layer), it is possible to buffer the system by the addition of 3 equivalents of sodium hydrogen carbonate, which can lead to better yields in cases where a base-labile substrate is used or where a base-labile product is formed.

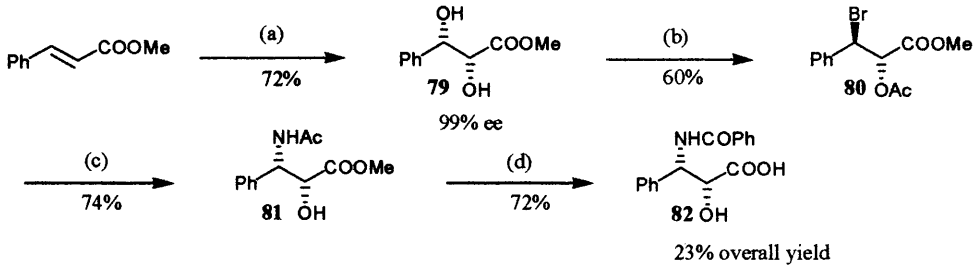
1.3.4 Substrates for the Asymmetric Dihydroxylation Reaction

Osmium catalysts are well known to be efficient for asymmetric dihydroxylation of alkenes; the reaction conditions tolerate many substituent groups, including alkyl, aryl and electron-withdrawing groups, additionally, mono-, di-, tri- and some tetrasubstituted alkenes react well. Asymmetric dihydroxylation is one of the simplest catalytic asymmetric reactions to perform. The reaction is completely insensitive to water and oxygen and can be performed in an open vessel in the range of 0-25 °C. The reactivity of the catalyst means that only a small amount is required and the reaction generally proceeds in very high yields.

Reports have shown that *trans*-alkenes lead to higher enantiomeric exess (70-90 %) relative to the *cis*-alkenes (< 25 %) which react very poorly; this may be attributed to steric hindrance of the *cis*-alkenes affecting binding of the catalyst. Osmium-catalysed AD of various enynes have been reported by Sharpless and co-workers,[70,71] and although it is known that triple bonds can be oxidized to the corresponding α-diketones by OsO_4, all reactions showed excellent chemoselectivity, *i.e.* yne-diol was observed as the sole product under the reaction conditions.

The hydrolysis of the intermediate osmate(VI) glycolate product can be accelerated by $MeSO_2NH_2$ (1 equivalent is normally added to the reaction mixture); this results in higher turnover rates, allowing the reaction to be run at 0 °C instead of 20 °C, thereby improving the enantioselectivity of the reaction. However, for terminal (monosubstituted and 1,1-disubstitued) alkenes $MeSO_2NH_2$ causes the rate of reaction to slow down.

Sharpless AD has been used in the synthesis of the side chain of taxol (Scheme 1.32), an essential structural unit for its biological properties.[72,73] The low cost and ease of this reaction allows the large-scale preparation of enantiomerically enriched substrates, such as **82** in high yields and excellent ee.



Scheme 1.32. *Reagents and conditions:* (a) (i) $(DHQ)_2PHAL$ (0.5 mol%), $K_2OsO_2(OH)_4$ (0.2 mol%) NMO (1.45 eq.), *t*-BuOH, (ii) recrystallise from toluene; (b) (i) $MeC(OMe)_3$, *p*-TsOH, (ii) MeCOBr; (c) (i) NaN_3, DMF, 50 °C, 19 h, (ii) H_2, Pd-C, MeOH; (d) (i) 10% HCl aq (ii) PhCOCl.

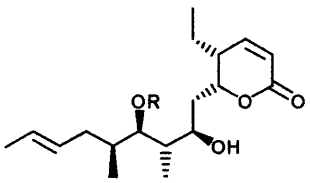
1.3.5 Asymmetric Dihydroxylation of Electron-Deficient Olefins

As OsO_4 is an electrophilic reagent, the rate of osmylation of electron-deficient olefins such as α,β–unsaturated carbonyl compounds can be very slow. The dihydroxylation of enones is achieved using fortified ADmix,[74] containing 1 mol% of $[K_2OsO_2(OH)_4]$ (instead of the usual 0.2-0.4 mol%) and 1 mol% of ligand. Also, in order to prevent base-induced epimerisation, the reaction should be buffered with 3 equivalents of sodium hydrogen carbonate.

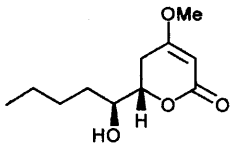
Unsaturated amides are poor substrates of the AD reaction under normal conditions (*i.e.* 0.2-0.4 mol% OsO_4 and 1 mol% of ligand). However, the dihydroxylation of amides in the presence of 1 mol% of $[K_2OsO_2(OH)_4]$, 5 mol% of ligand and unsaturated equivalent of $MeSO_2NH_2$ takes place rapidly and in high enantiomeric excesses.[75]

1.4 Aim of the Project

The 5,6-Dihydropyran-2-one ring is present in the plant growth regulator NK10958P **83** and the closely related immunosuppressant and cytotoxic agent pironetin **84**[76] (which differs from **83** by the presence of a methoxy group in place of the 4'-hydroxy group). The relatively simple structure of pironetin **84**, together with its potent biological activity have made it a synthetic target for different groups[77-80] and five total syntheses of pironetin have been reported in the past seven years.



R = H, NK10958P **83**
R = Me, Pironetin **84**



(-)-Pestalotin **85**

Scheme 1.33: 5,6-Dihydropyran-2-one ring-containing natural products.

Another synthetic target is the gibberellin synergist (-)-pestalotin **85**, which was isolated from *Pestaltia cryptomeriaecola* by Kimura and has also been obtained from an unidentified *Penicillium* species by Ellestad. Pestalotin has a 5,6-dihydro-4-methoxy-2*H*-pyran-2-one skeleton with one hydroxy group on the side chain; the absolute configuration is *6S, 1S*. Pestalotin is a biological pesticide and several total syntheses have been achieved, both racemic and single enantiomeric forms.

Chapters three and four describe the synthesis of important intermediates which can be applied to achieve the total synthesis of the natural products **83** and **85**. The main reactions used were Sharpless asymmetric dihydroxylation and Evans aldol methodology to allow the enantioselective synthesis of these intermediates.

Furthermore, the synthesis of the 3(*2H*)-furanone ring system is discussed in chapter 2 using Sharpless AD reaction followed by a mercury(II) catalysed reaction, which gave the dihydrofuranone product in high yields and good enantiomeric excesses.

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Chapter 2

The Enantioselective Synthesis of 3(*2H*)-Furanone Ring Systems

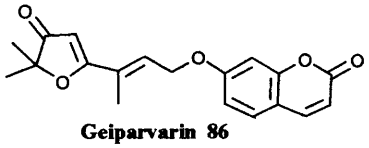
2.1 Introduction

The 3(*2H*)-furanone ring system is present in many natural products with varied and important biological properties, such as the antitumour agents geiparvarin **86**[1,2] and eremantholide **87**,[3-5] the antibacterial glycoside spinonin,[6] and numerous sesquiterpene natural products with anti-inflammatory activity.[7,8]

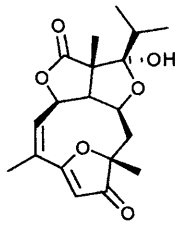
Geiparvarin **86** was isolated from the leaves of *Geijera parviflora* in 1967 and was reported to exhibit inhibitory activity against lymphocytic leukaemia. [9,10] It has been the subject of several synthetic investigations since its isolation.[11-16]

In 1975, Le Quesne and co-workers isolated a furanoheliangolide sesquiterpene (+)-eremantholide A **87** from the stems of the Brazilian plant *Eremanthus elaeagnus*,[17] it possesses cytotoxic activity against cells derived from human carcinoma of the nasopharynx *in vitro*.[18,19] The proposed structure (Figure 2.1) was confirmed by the first total synthesis of **87** carried out by Boeckmann and co-workers.[3]

The 3(*2H*)-furanone ring system is also present in other antitumour agents, namely jatrophone[20] and chilenone A,[21] it is believed that the ability of the 3(*2H*)-furanone ring to act as an alkylating agent by means of conjugate addition (*i.e.* as a Michael acceptor) is related to the antitumour properties of those compounds.[22]



Geiparvarin 86



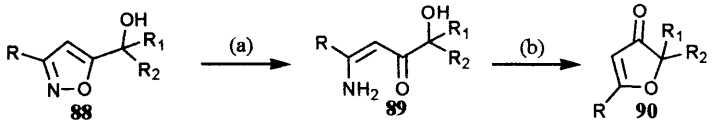
(+)-Eremantholide A 87

Figure 2.1: 3(*2H*)-Furanone-containing natural products

2.2 Literature Review of 3(2H)-Furanone Syntheses

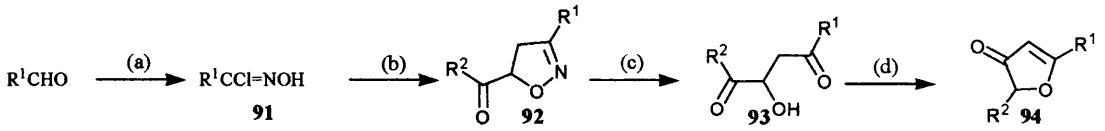
One of the most efficient routes to the 3(*2H*)-furanone ring system involves the acid-catalysed cyclisation-dehydration of an appropriately substituted α'-hydroxy-1,3-diketone,[16] however this route may be limited by the availability of the α'-hydroxy-1,3-diketone starting material.

Recently, a new route to substituted 3(*2H*)-furanones has been reported involving isoxazole chemistry (Scheme 2.1).[10] The catalytic hydrogenolysis of the isoxazole ring in **88** under mild conditions (*e.g.* H_2, PtO_2-Raney-Ni mixture) leads to fission of the labile nitrogen-oxygen bond, resulting in the formation of the β-aminoenone intermediate **89**, which can be considered as a synthetic equivalent of an α'-hydroxy-1,3-diketone. Acid-catalysed cyclisation of **89** then furnishes the 3(*2H*)-furanone. This route has been used in the synthesis of the natural product geiparvarin and its synthetic analogues.[2]



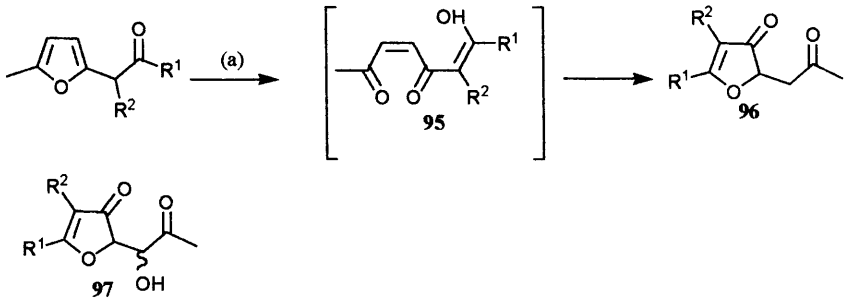
Scheme 2.1: Synthesis of 3(*2H*)-furanones using isoxazoles, (a) PtO_2-Raney-Ni, (b) AcOH: H_2O (2:1), 20 °C.

2-Isoxazolines such as **92** may also be converted into 3(*2H*)-furanones by catalytic reduction followed by acid-catalysed cyclisation (reflux in acetic acid with sodium acetate), Scheme 2.2.[23] Preparation of the 5-acyl-2-isoxazoline **92** was carried out by the cycloaddition of the hydroxamic acid chloride **91** with vinyl ketones ($R^2COCH{=}CH_2$), see Scheme 2.2.



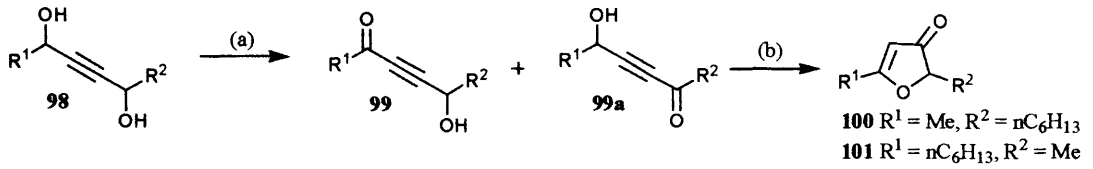
Scheme 2.2: The synthesis of 3(*2H*)-furanones from isoxazolines. (a) (i) H_2NOH, (ii) Cl_2, (b) Et_3N, $R^2COCH{=}CH_2$, (c) RaNi, EtOH: H_2O (1:1), 4 h, (d) AcOH, NaOAc (catalyst), 2-3 h, reflux, 55-65%.

A less successful method of dihydrofuranone synthesis uses *m*-chloroperoxybenzoic acid as an oxidising agent to convert furan derivatives into the 3(*2H*)-furanone **96**, possibly by an internal Michael addition of the enedicarbonyl intermediate **95**, (Scheme 2.3). However, over-oxidation to **97** in some examples led to diminished yields of the 3(*2H*)-furanone product (22-39%).[24]



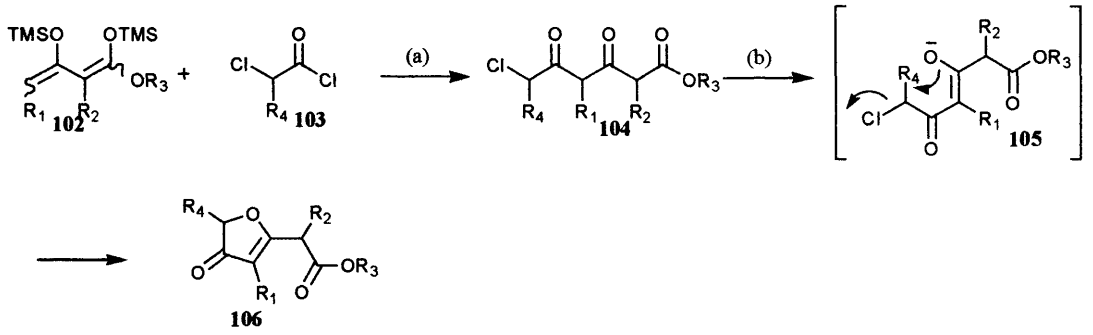
Scheme 2.3: The synthesis of 3(*2H*)-furanones using *m*-chloroperoxybenzoic acid, (a) 0.3 M *m*-CPBA, $CHCl_3$, 5 h, -10 °C, 55-75%.

Thomas and co-workers reported the synthesis of 3(*2H*)-furanones from 1-hydroxyalkynyl-2-yn-3-ones **99** using mild acidic conditions.[25] The hydroxy ynones **99** (and regioisomer **99a**) was prepared by oxidation of the corresponding acetylenic diol **98** using hydrogen peroxide and a tungsten-based catalyst. This method generated the 3(*2H*)-furanone product but as a mixture of regioisomers, **100** and **101**, which were then separated by column chromatography (Scheme 2.4).



Scheme 2.4: Preparation of 3(*2H*)-furanones from 1-hydroxyalkynyl-2-yn-3-ones (a) 30% aq. H_2O_2, Na_2WO_4, H_3PO_3, (b) 1% H_2SO_4.

Langer *et. al.*[26] reported that 6-chloro-3,5-dioxoesters **104** cyclise upon treatment with base (DBU), to give 3(*2H*)-furanones in moderate yields. 6-Chloro-3,5-dioxoesters **104** were synthesized by a chemo- and regio-selective reaction of 1,3-dianion synthons **102** with α–chlorocarboxylic acid chlorides **103** (Scheme 2.5).



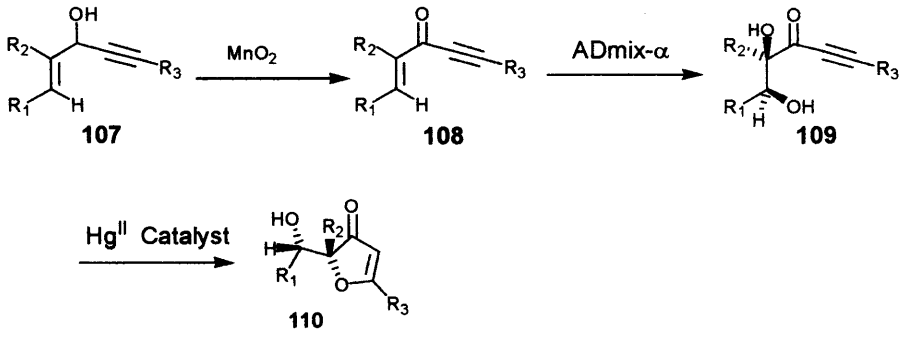
Scheme 2.5: Preparation of 3(*2H*)-furanones using 6-chloro-3,5-dioxoesters, (a) 0.3 equiv TMSOTf, CH_2Cl_2, -78 °C, (b) DBU, THF, 2 h, 65% overall.

The control of the relative and absolute stereochemistry of the 3(*2H*)-furanone ring is essential for the synthesis of a number of natural products such as (+)-eremantholide A **87**. The following section describes a new route for the enantioselective syntheses of 3(*2H*)-furanones from readily available starting materials.

2.3 Results and Discussions

2.3.1 Synthesis of 3(2H)-furanones using Mercury(II) Catalysis

This section discusses the enantioselective synthesis of 3(*2H*)-furanone ring systems of type **110** by the application of Sharpless asymmetric dihydroxylation on α,β-unsaturated alkynones **108**,[27-29] followed by mercury(II)-catalysed cyclisation[30] of the resulting diol **109** to afford **110** in good yields (50-97%) and high enantiomeric excesses (71-97% ee) (Scheme 2.6).

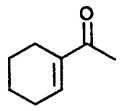
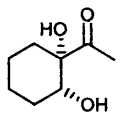
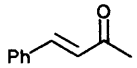
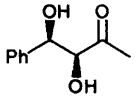
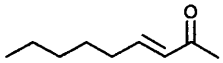
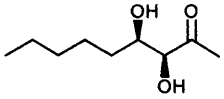
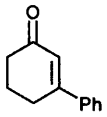
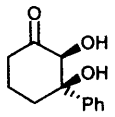


Scheme 2.6: A mercury$^{(II)}$ catalysed route to 3(2H)-furanones.

Whilst the asymmetric dihydroxylation (AD) of enones under Sharpless conditions have been reported with good yields and excellent enantiomeric excesses (Table 2.1),[31] the asymmetric dihydroxylation of enynones of type **108** has not been reported previously.

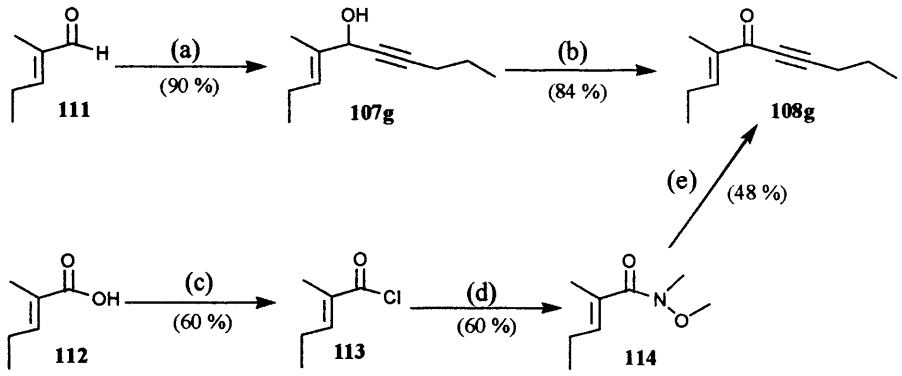
Different substitution patterns on the enynone **108** were used to establish the scope and limitations of the dihydroxylation and cyclisation reactions. The application of the mercury(II)-catalysed reaction to achieve the synthesis of a 3(*2H*)-furanone-containing natural product will be investigated. The use of a palladium(II) species in the cyclisation of diol **109** was investigated to form an alternative for the mercury(II) catalyst.

Table 2.1: Sharpless asymmetric dihydroxylation of α,β-unsaturated ketones.

Entry	Substrate	Product	Yield	%ee
1			73%	98
2			69%	92
3			87%	98
4			79%	82

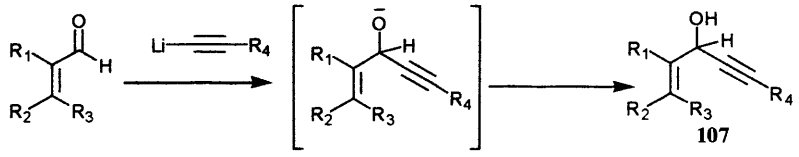
2.3.2. The Preparation of Enynones 108

α,β-Unsaturated ynones **108** were readily prepared using the routes outlined in Scheme 2.7; the first synthetic route generates **108** by MnO_2 oxidation of the corresponding alcohol **107**.[32] The second route led to **108** by a displacement reaction using the anion of a terminal alkyne and *N*-methyl-*N*-methoxy amide (Weinreb amide) **114**, itself prepared from the carboxylic acid **112**.[33] The former route gave better yields, and so was used to obtain the allylic alkynones required in this work. (Table 2.2)



Scheme 2.7: Preparation of enynones (a) pent-1-ynyl-lithium, THF, 20 °C, 3 h; (b) MnO_2, CH_2Cl_2, 20 °C, 24 h; (c) $SOCl_2$, CH_2Cl_2, 0 °C, 10 min then 60 °C; (d) MeONHMe.HCl, Pyridine, CH_2Cl_2, 0-20 °C; (e) pent-1-ynyl-lithium, THF, 20 °C, 3 h.

α-Alkynyl allylic alcohols of type **107** were prepared by the 1,2-addition of an alkyllithium to α,β-unsaturated aldehydes. The alkynyllithium was generated *in situ,* by the deprotonation of the terminal alkyne using *n*-butyllithium in anhydrous tetrahydrofuran under an inert atmosphere. After stirring for a short time (~ 0.5 h), the enal in a solution of distilled tetrahydrofuran was added dropwise. After completion of the reaction protonation of the resulting lithium enolate was achieved by addition of aqueous ammonium chloride (Scheme 2.8). Workup and evaporation of the solvents gave the crude material which was purified by flash column chromatography. This addition reaction resulted in good yields for all the substrates used.

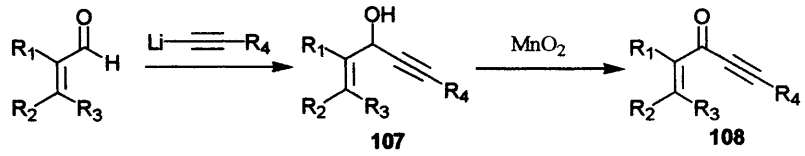


Scheme 2.8: Synthesis of α-alkynyl allylic alcohols **107**.

Table 2.2 summarizes the results for the alkynone synthesis, which were obtained in good to excellent yields from the corresponding aldehydes. The oxidation of **107** using manganese dioxide gave high yields of the enynone **108** and was carried out by adding a solution of **107** (1 equiv) in dichloromethane to a stirred suspension of

manganese dioxide (16 equiv) in dichloromethane under an atmosphere of nitrogen and the mixture was stirred at 20 °C until reaction completion (24 h).[32]

Table 2.2: Synthesis of enynones **108**.



107	R_1	R_2	R_3	R_4	Yield (%)	**108**	Yield (%)
a	H	H	H	^{n}Pr	96	**a**	75
b	Me	H	H	^{n}Pr	92	**b**	80
c	H	Et	H	^{n}Pr	90	**c**	92
d	H	Et	H	Ph	95	**d**	79
e	H	Me	H	^{n}Pr	85	**e**	74
f	H	Ph	H	^{n}Pr	99	**f**	97
g	Me	Et	H	^{n}Pr	93	**g**	95
h	Me	Et	H	Ph	94	**h**	90
i	Me	Et	H	OEt	90	**i**	78
j	Me	Ph	H	^{n}Pr	91	**j**	87
k	Me	Et	H	$-(CH_2)_3OH$	45[a]	**k**	84
l	Me	Et	H	$-(CH_2)_4OH$	68[a]	**l**	90
m	Me	Et	H	H	95[b]	**m**	73
n	Me	Et	H	CO_2Et	83[c]	**n**	85
o	H	Me	Me	^{n}Pr	74	**o**	71
p	H	Me	Me	Ph	75	**p**	74
q	$(CH_2)_3$		H	OEt	66	**q**	80

[a] In the cases of **107k** and **107l**, 2 equivalents of *n*-butyllithium were used to generate the double anion thus making it unnecessary to protect the hydroxyl group and the lower yield may be a result of poor selectivity of the two nucleophilic sites. [b] Alkynyl allylic alcohol **107m** was prepared by the addition of commercially available ethylmagnesium bromide to 2-methylpent-2-enal, which proceeded in a high yield (95 %) using the procedure reported by Spino, and co-workers.[34] [c] For the synthesis of **107n** the procedure reported by Crimmins

and co-workers was applied, using lithium diisopropylamide (LDA) as the base, instead of the usual *n*-butyllithium.[35,36]

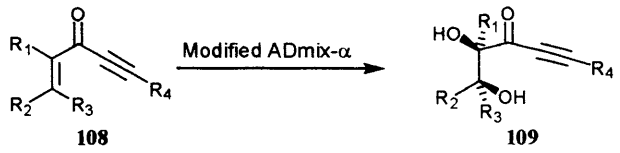
2.3.3 Synthesis of 2,3-Dihydroxy Alkynones

The Shapless asymmetric dihydroxylation (AD) reaction is widely used in natural product synthesis because of its convenience and tolerance of a wide range of functional groups. The dihydroxylation requires a sub-stoichiometric osmium catalyst and the use of an oxidant to regenerate the catalyst, namely $K_3Fe(CN)_6$ (3 equiv). The stereofacial selectivity of the dihydroxylation is determined by the chiral ligand used (such as $(DHQ)_2$-PHAL). Another reagent required in this reaction is potassium carbonate which acts as a buffer. A premix of the Sharpless AD reagents are commercially available as ADmix-α and ADmix-β depending on the chiral ligand present. For di- and tri-substituted enynones it was necessary to add one equivalent of methane sulphonamide to aid the cleavage of the product from the intermediate osmium ester.

Since α,β-unsaturated carbonyl compounds were reported to be poor substrates for the original Sharpless asymmetric dihydroxylation reaction,[31] modified ADmix was used for the dihydroxylation of alkynones **108**. This method, described by Sharpless and co-workers, involved the addition of higher loadings of the osmium catalyst (to increase the total to 1 mol% with respect to the alkynone substrate) also the addition of sodium hydrogen carbonate (3 equiv) which is used as a buffer to prevent possible side-reactions of the ketone product, such as epimerization of the α-asymmetric centre and retro-aldol fragmentation.

The enantiomeric excesses (ee) of the diols **109** (Table 2.3) were not determined at this stage as it was expected that the ees of the corresponding 3(*2H*)-furanone could give a good indication of the overall selectivity of this synthetic route.

Table 2.3: Synthesis of 2,3-dihydroxyalkynones.



108 **109**

108	R_1	R_2	R_3	R_4	**109**	Yield (%)
a	H	H	H	^{n}Pr	**a**	-
b	Me	H	H	^{n}Pr	**b**	81
c	H	Et	H	^{n}Pr	**c**	50
d	H	Et	H	Ph	**d**	47
e	H	Me	H	^{n}Pr	**e**	53
f	H	Ph	H	^{n}Pr	**f**	-
g	Me	Et	H	^{n}Pr	**g**	95
h	Me	Et	H	Ph	**h**	66
j	Me	Ph	H	^{n}Pr	**j**	-
k	Me	Et	H	$-(CH_2)_3OH$	**k**	-
l	Me	Et	H	$-(CH_2)_4OH$	**l**	-
m	Me	Et	H	H	**m**	-
n	Me	Et	H	CO_2Et	**n**	-
o	H	Me	Me	^{n}Pr	**o**	-
p	H	Me	Me	Ph	**p**	-

Unsubstiuted enynones:

The Sharpless AD was attempted using alkynone **108a**, with the conditions described above; however, this reaction was unsuccessful and only the starting material was isolated.

*The 1,1-disubstituted enynone **108b**:*

The 1,1-disubstituted alkynone **108b** underwent Sharpless asymmetric dihydroxylation rapidly, giving diol **109b** in 81% yield. The crude material was sufficiently pure to be used without further purification.

1,2-Disubstituted enynones:

Addition of more of the chiral ligand (increased to 1.0 mol%), *i.e.* $(DHQ)_2$-PHAL for ADmix-α or $(DHQD)_2$-PHAL in the case of ADmix-β as well as the osmium catalyst (1.0 mol%) was required to allow the reaction to reach completion and to improve the yields of 1,1-disubstituted enynones **108c-e**. The AD reaction was unsuccessful in the case of phenyl-substituted **108f**.

1,1,2-Trisubstituted enynones:

The asymmetric dihydroxylation of the ynones **108g** and **108h** gave high and moderate yields of the diols **109g** and **109h** respectively. However, the AD reaction of **108j** was unsuccessful and only recovered starting material was obtained. In the case of **108k** and **108l** a complex mixture was obtained.

Electron-withdrawing groups, such as CO_2Et, attached to the alkyne and terminal alkynones resulted in no reaction under the Sharpless asymmetric dihydroxylation method and only the starting materials **108m** and **108n** were detected by TLC. This poor reactivity could be explained in terms of the electron-deficiency of the double bond.

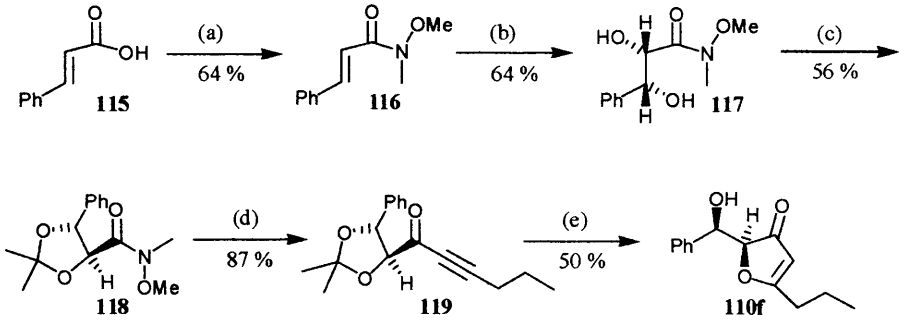
1,2,2-Trisubstituted enynones:

The dihydroxylation of 1,2,2-trisubstituted ynones **108o** and **108p** was unsuccessful and only starting materials were recovered; this may be due to steric hindrance of the alkynone.

2.3.3.1 Synthesis of 3(*2H*)-Furanones *via* Asymmetric Dihydroxylation of Weinreb Amides

The enynones derived from cinnamaldehyde, such as **108f**, were found to be poor substrates for the Sharpless AD reaction; therefore an alternative route was devised for the preparation of the furanone system (Scheme 2.9). The asymmetric dihydroxylation of the corresponding Weinreb amide **116** was reported to give the diol **117** in 93% enantiomeric excess (ee).[37] Then the alkynylation of the acetonide **118** gave the protected ynone **119** in 87% yield,[33,38] which underwent concomitant deprotection and cyclisation upon treatment with aqueous acidic mercury(II) to give

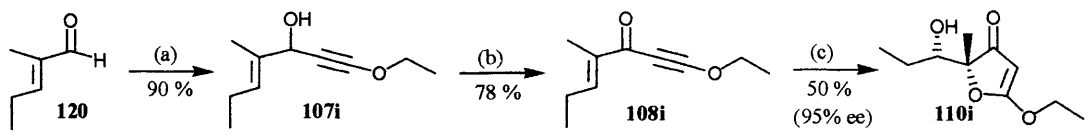
110f. This route could be applied to obtain the 3(*2H*)-furanones in cases where the dihydroxylation of the enynone was unsuccessful.



Scheme 2.9: An alternative route to 3(*2H*)-furanones, via the Weinreb amide, (a) (i) ^{i}BuOCOCl, NMM, CH_2Cl_2, 0 °C, 20 min (ii) MeONHMe.HCl, 20 °C, 2 h, (b) modified ADmix-β, $(DHQ)_2$-PHAL (5 mol%), ^{t}BuOH: H_2O (1:1), 0 °C, 24 h, (c) 2,2-dimethoxypropane: DMF (1:1), *p*-TsOH.H_2O (cat.), 20 °C, 24 h, (d) pent-1-ynyl-lithium, THF, 20 °C, 3 h, (e) HgO/ H_2SO_4, acetone, 20 °C, 20 min.

2.3.3.2 Preparation of 4-Ethoxy-Substituted 3(*2H*)-Furanones

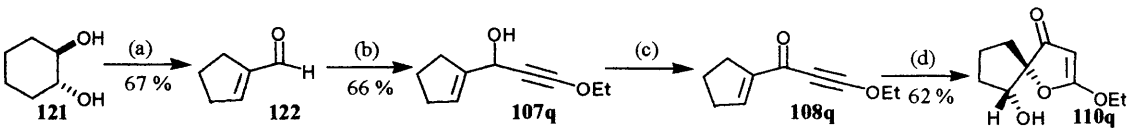
Further investigation of the effect of substitution on the alkyne moiety showed that electron-donating groups such as the ethoxy group caused spontaneous cyclisation of the dihydroxy ynones after the Sharpless AD reaction, thus allowing the mercury-catalysed step to be omitted. The treatement of enynone **108i** with the ADmix reagents gave the 3(*2H*)-furanone **110i** in 50 % yield (Scheme 2.10).



Scheme 2.10: Preparation of 3(*2H*)-furanone **110i**, (a) ethoxyethynyl-lithium, THF, 20 °C, 3 h, (b) MnO_2, CH_2Cl_2, 20 °C, (c) modified ADmix-α, $MeSO_2NH_2$, $NaHCO_3$, ^{t}BuOH: H_2O (1:1), 0 °C, 24 h.

Similarily, the spiroketone **110q** was synthesised from enynone **108q** using the Sharpless AD reaction, which generated the 3(*2H*)-furanone product in 62% isolated

yield after column chromatography (Scheme 2.11). The starting aldehyde **122** was obtained from the commercially available cyclohexane-1,2-diol using the method reported by Brown and co-workers.[39]



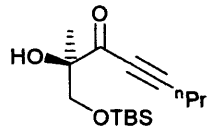
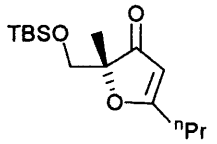
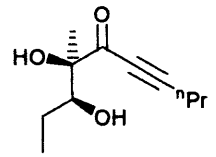
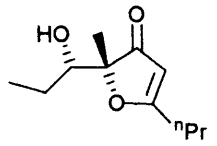
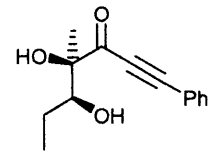
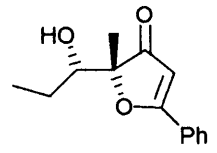
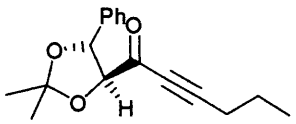
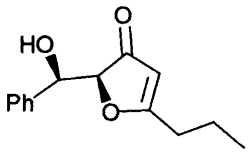
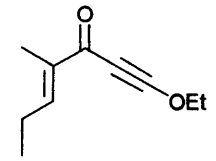
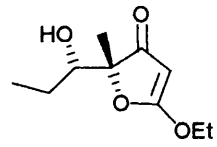
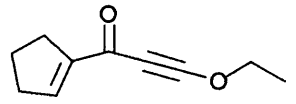
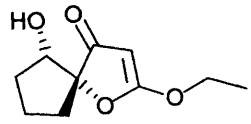
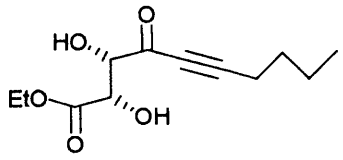
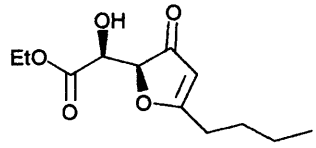
Scheme 2.11: Synthesis of spiroketone **110q** using Sharpless asymmetric dihydroxylation, (a) $NaIO_4$, KOH(aq) (b) ethoxyethynyl-lithium, THF, 20 °C, 3 h, (c) MnO_2, CH_2Cl_2, 20 °C, (d) modified ADmix-α, $MeSO_2NH_2$, $NaHCO_3$, ^tBuOH: H_2O (1:1), 0 °C, 24 h.

2.3.4 Mercury(II)-Catalysed Cyclisations

The enantiopure alcohols prepared using the Sharpless asymmetric dihydroxylation reaction, as described in section 2.3.3, were treated with the mercury(II) catalyst in acidic solution which resulted in the formation of the 3(*2H*)-furanone products in good yields and excellent enantiomeric excesses, the results are summarised in Table 2.4. The racemic 3(*2H*)-furanone **110h** was used as a reference sample for the ee determination of the enantiopure furanones. It was prepared using the osmium-based catalyst, *N*-methylmorpholine *N*-oxide, and citric acid additive, this procedure, described by Sharpless and co-workers,[40] is a modification to the Upjohn procedure which permits the dihydroxylation of electron-deficient olefins, the resultant diol was cyclised using the mercury(II) oxide catalyst to furnish ***rac*-110h**.

X-ray analysis was performed on the 3(*2H*)-furanone **110h** which supported the fact that the product was the 5-membered 3(*2H*)-furanone and not the 6-membered dihydropyranone ring (See Appendix A for the crystal data and structural assignment). This result was in agreement with the ^{13}C NMR of the cyclised products, as the ^{13}C peak of the carbonyl group was usually in the region of 206-210 ppm, whilst for the dihydropyranone ring it is typically in the region of 197-198 ppm.[30]

Table 2.4: Synthesis of 3(*2H*)-furanones

Entry	Starting Material	3(*2H*)-Furanone	Yield (%)	ee (%)
1	 **109b**	 **110b**	93	91[a]
2	 **109g**	 **110g**	80	92[b]
3	 **109h**	 **110h**	97	97[b]
4	 **119**	 **110f**	50[d]	97[b]
5	 **108i**	 **110i**	50[c]	95[b]
6	 **108q**	 **110q**	62[c]	71[a]
7	 **142**	 **143**	62	d.r. 6:4

[a] Enantiomeric purity was determined by ^{1}H NMR analysis of the Mosher's ester derivative.

[b] Enantiomeric purity was determined by HPLC analysis using a chiralcel OJ column (entries

2 and 3) and chiralcel OD column (entries 4 and 5). [c] For the terminal ethoxy-substituted enynone **110i** and **110q**, dihydroxylation of the double bond using Sharpless AD conditions led to spontaneous cyclisation to the 3(*2H*)-furanone. [d] Overall yield for two steps, *i.e.* deprotection of diol and mercury-catalysed cyclisation.

2.3.5 Determination and Optimisation of Enantiomeric Excess (ee)

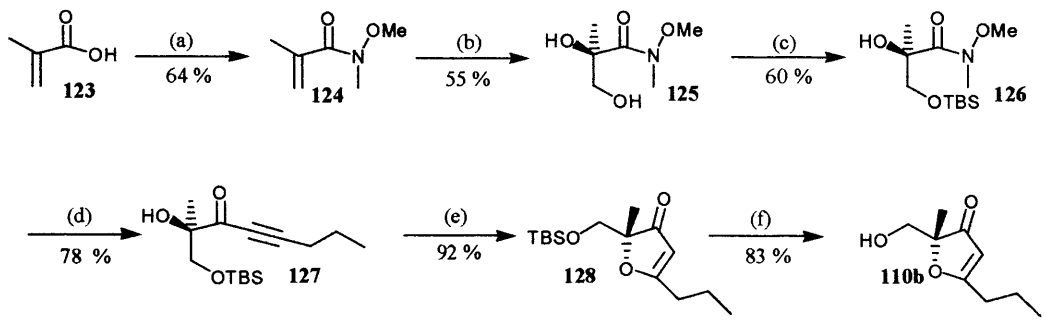
Enantiomeric excesses of the 3(*2H*)-furanones were determined either by chiral HPLC analysis or by ^{1}H NMR analysis of the Mosher ester derivatives. In both cases the racemic 3(2*H*)-furanone prepared by osmylation of the enynone followed by the mercury(II) cyclisation was used as the reference.

The optical purity of **110h** was determined by HPLC analysis using a Chiralcel OJ column (50:50 ethanol;hexane, λ = 210 nM). Racemic **110h** gave two separate peaks with retension times of 5.32 and 6.84 min. The major enantiomer of the chiral **110h** eluted after 5.32 min and the optical purity was calculated to be 97% ee using the ratio of the estimated peak areas.

The optical purity of **110f**, **110g** and **110i** was determined using HPLC analysis with a Chiralcel OD column (0.46 cm x 5 cm, eluent: 10:90 2-propanol: hexane, flow rate: 0.7 ml/ min, detection: UV 254 nm).

The Mosher's ester derivatives[41-44] of **110b** and **110q** were prepared using the commercially available α-methoxy-α-trifluoromethylphenyl acetyl chloride, (*S*)-MTPACl, (DMAP, CH_2Cl_2, 20 °C).[41] This allowed the quantitative determination of the enantiomeric composition of the chiral 3(*2H*)-furanone product.

In the case of furanone **110b** a poor ee (47%) was obtained when the usual synthetic route was applied, *i.e.* the Sharpless asymmetric dihydroxylation of the enynone **108b** followed by the mercury(II)-catalysed cyclisation. However, an ee of 91% was obtained for **110b** prepared by the dihydroxylation of the corresponding Weinreb amide **124**,[45,46] followed by the alkynylation of the mono protected amide **126**, and finally mercury(II) catalysed ring-closure (Scheme 2.12).



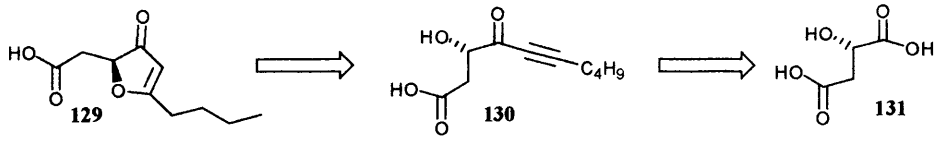
Scheme 2.12: A highly enantioselective route to 3(*2H*)-furanone **110b**, (a) (i) ^{i}BuOCOCl, NMM, CH_2Cl_2, 0 °C, 20 min (ii) MeONHMe.HCl, CH_2Cl_2, 20 °C, 2 h, (b) modified ADmix-α (contains 1 mol% of the osmium catalyst), $(DHQ)_2$-PHAL (5 mol%), ^{t}BuOH: H_2O (1:1), 0 °C, 24 h, (c) TBSCl, imidazole, CH_2Cl_2, 20 °C, 14 h, (d) pent-1-ynyl-lithium, THF, 20 °C, 3 h, (e) HgO/ H_2SO_4, acetone, 20 °C, 20 min, (f) $HCl_{(aq)}$, MeOH, 20 °C, 24 h.

2.3.6 Synthesis of a 3(2H)-Furanone-Containing Natural Product

2.3.6.1. Enantioselective Synthesis of the Natural Product 129 using (S)-Malic acid

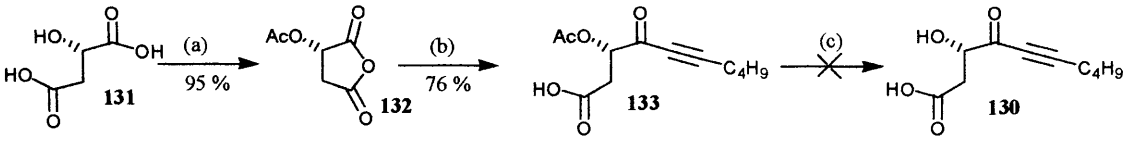
The 3(*2H*)-furanone **129** (Scheme 2.13) was recently isolated from *Erigeron annuus*.[47] It is a secondary metabolite produced to affect the growth and germination of other plant species thereby eliminating competing plants. Such compounds are known as allelochemicals and have potential uses as effective and environmentally friendly agrochemicals.

The strategy for the synthesis of the plant growth regulator **129** involved the cyclisation of the alcohol **130** by treatment with the mercury(II) catalyst in acidic solution.

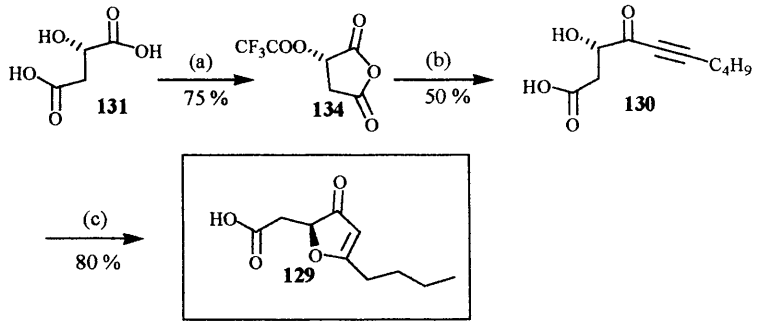


Scheme 2.13: Proposed synthesis of **129** from (*S*)-malic acid.

The attempted synthesis of alcohol **130** via deprotection of the acetate **133** with potassium carbonate was unsuccessful (Scheme 2.14) as it resulted in degradation of the starting material. The convenience of proceeding from (*S*)-malic acid **131** via its anhydride acetate **132** and then ring-opening of the latter to give **133** suggested that an alternative and more readily cleavable ester, the TFA ester **134** could succeed (Scheme 2.15). It was found that addition of the lithium acetylide to **134** not only led to the ynone, but also deacylated the ester functionality, leading in one step to **130**, the mercury(II) catalysed cyclisation furnished **129**.



Scheme 2.14: Attempted preparation of the ynone **130**, (a) AcCl, 40 °C, 2 h, (b) hex-1-ynyl-lithium, 20 °C, THF, 3 h, (c) K_2CO_3, THF, 20 °C.

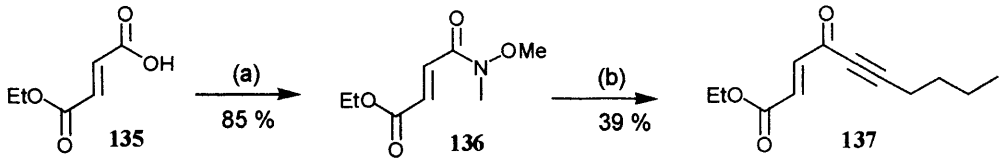


Scheme 2.15: Synthesis of the natural product **129**, (a) TFAA, 0 °C, (b) hex-1-ynyl-lithium, THF, 20 °C, 3 h, (c) HgO/ H_2SO_4, acetone, 20 °C, 20 min.

The stereochemistry of the asymmetric centre in the natural product follows from (*S*)-malic acid used as the starting material and the enantiomeric purity was confirmed by measuring the optical rotation of **129**, which was found to be comparable to the literature value, (measured $[\alpha]_D = +25.0$ (c 0.03, MeOH); lit $[\alpha]_D = +29.0$ (c = 0.07, MeOH)).[47]

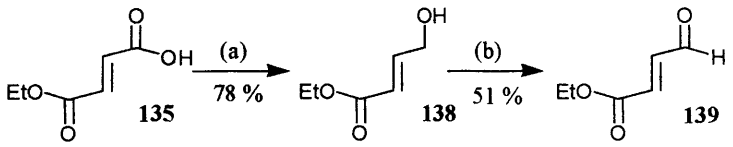
2.3.6.2 An Alternative Approach to the Synthesis of 3(2H)-Furanone 129 using Sharpless Asymmetric Dihydroxylation

The asymmetric synthesis of the 3(*2H*)-furanone natural product **129** using the Sharpless AD reaction. The preparation of enynone **137** by alkynylation of the Weinreb amide **136** resulted in a poor yield and very impure material, possibly due to poor regioselectivity, as the acetylide anion can also react with the ester functionality (Scheme 2.16).[48]



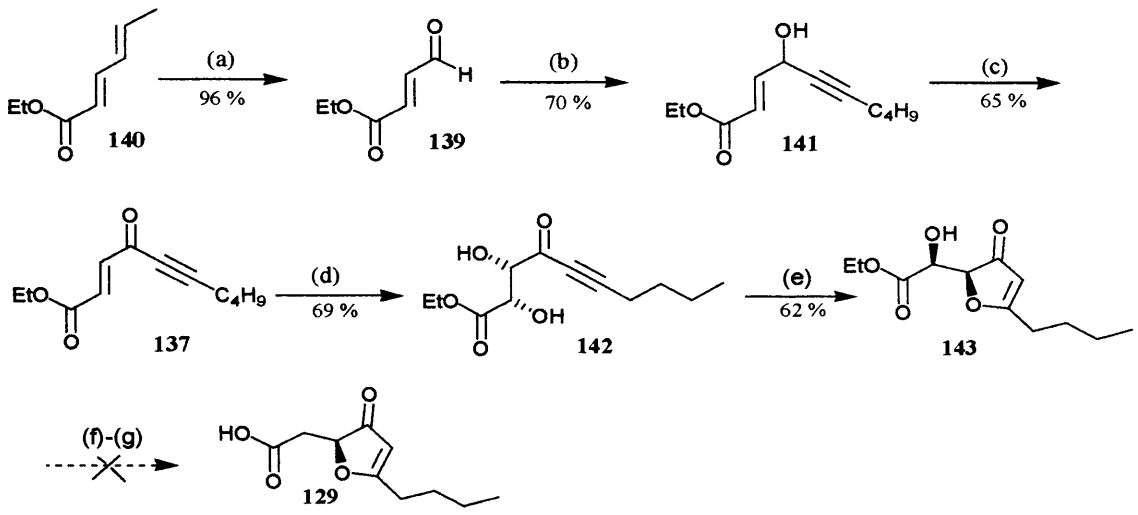
Scheme 2.16: Preparation of enynone **137**, (a) (i) ^{i}BuOCOCl, NMM, CH_2Cl_2, 0 °C, 20 min (ii) MeONHMe.HCl, CH_2Cl_2, 20 °C, 2 h, (b) hex-1-ynyl-lithium, THF, -78 °C, 1 h,

The synthesis of enynone **137** from the corresponding aldehyde **139** gave better yields and higher purity of the crude material. The aldehyde was prepared by selective reduction of the half-ester **135**[49,50] (Scheme 2.17), or more conveniently by the selective ozonolysis of ethyl sorbate **140** (Scheme 2.18).[39;51;52]



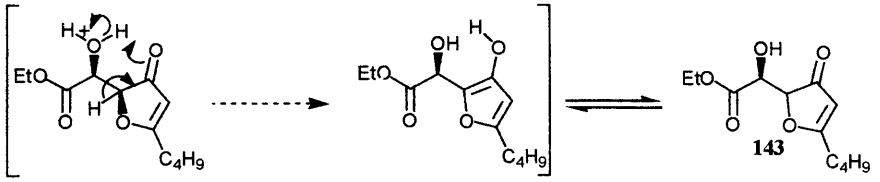
Scheme 2.17: Synthesis of the aldehyde **139** from the half-ester **135**, (a) $BH_3.Me_2S$, THF, 0 °C, (b) MnO_2, CH_2Cl_2, 20 °C.

Scheme 2.18 describes the proposed route towards the natural product **129**, using the aldehyde **139**, which was prepared by selective ozonolysis of ethyl sorbate. The alkynylation reaction of **139** proceeded rapidly and with greater selectivity (cf. the Weinreb amide) and thus resulted in a satisfactory sample of alcohol **141** which was oxidised to enynone **137** using manganese dioxide.



Scheme 2.18: Towards the synthesis of **129**. *Reagents and conditions*: (a) O_3, Me_2S, Sodan-19 indicator, (b) hex-1-ynyl-lithium, THF, - 78 °C, 1 h, (c) MnO_2, CH_2Cl_2, 20 °C, 24 h, (d) modified ADmix-β, $MeSO_2NH_2$, $NaHCO_3$, ^tBuOH: H_2O (1:1), 0 °C, 24 h, (e) HgO/ H_2SO_4, acetone, 20 °C, 20 min, (f) (i) Thiocarbonyldiimidazole, THF, 65 °C, 12 h, 57%, (ii) Bu_3SnH, AIBN, toluene, 75 °C, 90 min, (g) LiOH: H_2O, THF, 20 °C.

The furanone **143** was obtained in good yields, however it's ^1H NMR showed that it underwent epimerisation, possibly prompted by the acidic conditions of the cyclisation step (Scheme 2.19). Furthermore, attempts to deoxygenate **143** using Barton-McCombie conditions were unsuccessful,[53-55] possibly because of the high temperatures involved which may have led to degradation of the starting material.

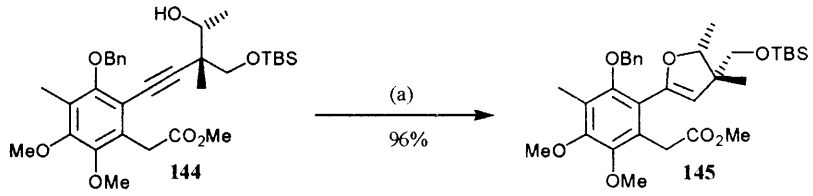


Scheme 2.19: Epimerisation of 3(*2H*)-Furanone **143** at the C2 position.

2.3.7 Palladium(II)-Catalysed Cyclisation leading to 3(2H)-Furanones

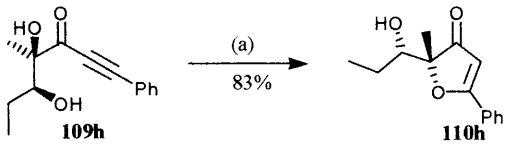
Due to the high toxicity of the Mercury catalyst alternative conditions for the cyclisation of α,β-dihydroxy alkynones into the 3(*2H*)-furanone were sought, such as the use of palladium(II)-based catalysts described below.

Palladium(II) chloride (20 mol%) was applied by Saito and co-workers to effect the cyclisation of a β-hydroxy alkyne **144** into the dihydrofuran product **145** in 96% yield (Scheme 2.20).[56]



Scheme 2.20: *Reagents and conditions*: (a) 20 mol% $PdCl_2$, THF, 20 °C, 3.5 h.

Given this precedence, the cyclisation of the diol **109h** was attempted using 20 mol % of $PdCl_2$ (THF, 20 °C, 1 h) this gave a 92% yield of the 3(*2H*)-furanone **110h** as the sole product. The reaction was also performed using 2 mol% of $PdCl_2$ which gave an 83% yield of **110h** after 24 h (Scheme 2.21). The high yields, convenience and safety of this method make it preferable to the mercury(II)-catalysed reaction. However, due to time limitations this reaction was not applied for the other diols.



Scheme 2.21: Palladium(II)-catalysed cyclisation of dihydroxy alkynones. (a) $PdCl_2$, THF, 20 °C, 24 h.

2.4 Conclusions

A novel method for the preparation of 3(*2H*)-furanone ring systems using the Sharpless asymmetric dihydroxylation reaction was described. The cyclisation to the 3(*2H*)-furanone ring was achieved by using either a catalytic amount of acidic mercury(II) oxide or by using a palladium(II) catalyst. This synthesis used readily available starting material and proceeded with good yields and high enantiomeric excesses, and so it may be applied for the enantioselective synthesis of furanone-containing natural products.

In the case of ethoxy substituted alkynones, such as **108i** and **108q**, the asymmetric dihydroxylation of the enynone under Sharpless's conditions resulted in simulataneous cyclisation to the 3(*2H*)-furanone product. In all the examples investigated the mercury(II)-catalysed cyclisation proceeded cleanly to generate the 3(*2H*)-furanone as the sole product with non of the 6-membered dihydropyranone product being formed.

Experimental

Thin-layer chromatography (TLC) analyses were performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and components were visualized by illumination with UV light or by staining with aqueous potassium permanganate. Flash column chromatography was performed using Merck 0.040 to 0.063 mm, 230 to 400 mesh silica gel. ^{1}H NMR spectra were recorded on a 300 MHz Bruker AC300 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane (TMS), using residual chloroform (7.27 ppm) as an integral standard. The following abbreviations are used to describe NMR signals: δ, chemical shift; s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; b, broad, coupling constants *J* are given in Hertz (Hz). ^{13}C NMR were recorded on a 300 (75 MHz) Bruker AC300 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an integral standard. Infrared (IR) spectra were recorded on a Perkin-Elmer PE-983 spectrophotometer: absorption frequencies were recorded in wavenumbers (ν_{max} in cm^{-1}). Mass spectra were obtained by using a VG7070H mass spectrometer with Finigan Incos II operating in chemical ionization (CI) and electron impact (EI) modes, as specified in the text. Molecular ion peaks (M^+), base peaks and other major peaks are reported.

Starting materials were purchased from Aldrich or Lancaster. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use and dichloromethane was distilled from calcium hydide. Ether refers to diethyl ether and petroleum ether refers to 40-60 °C fractions of petroleum ether. All glassware was oven-dried, assembled hot and cooled under a stream of nitrogen gas before use. Reactions with air-sensitive materials were carried out by standard syringe techniques. Temperatures of – 78 °C were obtained by the addition of dry ice to acetone. Evaporation refers to the removal of solvent under reduced pressure.

(*E*)-4-Methyldec-3-en-6-yn-5-ol (107g). A solution of pent-1-yne (0.71 g, 1.0 mL, 10.4 mmol) in dry tetrahydrofuran (26 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (4.5 mL, 11.4 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-2-methylpent-2-enal (0.93 g, 1.08 mL, 9.8 mmol) in dry tetrahydrofuran (13 mL). The mixture was stirred for a further 3 h, and then poured into saturated aqueous ammonium carbonate (11.5 mL). The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel (5:95 ethyl acetate: petroleum ether) to give **107g** (1.19 g, 76%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3362 (OH), 2206 (alkyne group), 1626 (C=C); ^1H NMR δ_H 5.60 (1H, t, J = 7.1, C=*CH*), 4.74 (1H, s, *CH*OH), 2.21 (2H, m, CH_2), 2.06 (2H, pentet, J = 7.5, CH_2), 1.74 (3H, s, CH_3), 1.58 (2H, sextet, J = 7.5, CH_2), 0.98 (6H, t, J = 7.5, CH_3); ^{13}C NMR δ_C 134.6 (CH=*C*CH_3), 129.9 (*CH*=CCH_3), 86.6 (*C*≡CCO), 80.3 (C≡*C*CO), 68.5 (COH), 22.4 (CH_2), 21.3 (2 x CH_2), 14.4 (CH_3) 14.3 (CH_3) 13.7 (CH_3); LRMS m/z (%)+EI 166 (M^+, 20%), 151 (10), 137 (100), 109 (10), 95 (30), 91 (15), 69 (23), 56 (25), 43 (57), 32 (15); HRMS calcd for $C_{11}H_{18}O$ 166.1358, found 166.1355.

(*E*)-2-Methyl-pent-2-enoyl chloride (113). To a solution of (*E*)-2-methyl-2-pentenoic acid (2.0 g, 14.1 mmol) in dichloromethane (100 mL) cooled in an ice-bath under nitrogen, thionyl chloride (3.2 g, 4 mL, 33.6 mmol) was added dropwise with stirring. The mixture was then heated under reflux at 60 °C (under nitrogen). After the reaction was complete, indicated by TLC analysis, the solvent and excess thionyl chloride were evaporated under reduced pressure at 40 °C to give **113** (~2.0 g) as a dark brown oil, which was used directly in the next step; IR ν_{max} (cm^{-1}) 1800 (COCl).

(*E*)-2-Methylpent-2-enoic acid *N*-methoxy-*N*-methyl amide (114). To a solution of (*E*)-2-methylpent-2-enoyl chloride (2.58 g, 16.4 mmol) in dichloromethane (50 mL) at 0 °C was added *N*, *O*-dimethylhydroxylamine hydrochloride (1.88 g, 19.3 mmol) followed by pyridine (3.05 g, 2.9 mL, 38.5 mmol). The mixture was stirred at 20 °C and progress of the reaction was monitored by TLC. On completion, the reaction was acidified using aqueous hydrochloric acid (20 mL, 2 M), and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined

organic layers were washed with saturated aqueous sodium hydrogen carbonate (2 x 60 mL) followed by brine (60 mL). The solution was dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (30:70 ether: petroleum ether) to give **114** (1.3 g, 60%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 1740 (C=O), 1621 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.80 (1H, t, J = 7.0, *CH*=C), 3.61 (3H, s, OCH_3), 3.20 (3H, s, NCH_3), 2.12 (2H, q, J = 7.5, *CH*$_2$CH=), 1.84 (3H, s, CH_3), 1.05 (3H, t, J = 7.5, CH_2*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (C=O), 135.6 (CH=*C*), 130.5 (*CH*=C), 60.9 (OCH_3), 33.8 (NCH_3), 21.1 (CH_2), 13.8 (CH_3) 13.3 (CH_3); LRMS m/z (%)+CI 158 (M+H, 3%), 111 (2), 97 (100), 82 (2), 74 (2), 69 (60), 61 (3), 56 (18); HRMS calcd for $C_8H_{15}O_2N$ 158.11808 (M+H), found 158.11783.

(*E*)-4-Methyldec-3-en-6-yn-5-one (108g). *Method A*: A solution of 4-methyldec-3-en-6-yn-5-ol (0.60 g, 3.6 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (6.36 g, 74.1 mmol, 16 eq.) in dichloromethane (60 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108g** (0.50 g, 83%) as a colourless oil; IR ν_{max} (cm^{-1}) 2201 (alkyne group), 1694 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.32 (1H, t, J = 7.5, C*H*=C), 2.61 (2H, t, J = 7.0, C≡CC*H*$_2$), 2.54 (2H, pentet, J = 7.5, *CH*$_2$CH=C), 2.02 (3H, s, C=CC*H*$_3$), 1.89 (2H, sextet, J = 7.0, CH_2*CH*$_2$$CH_3$), 1.34 (3H, t, J = 7.5, C=CHCH_2*CH*$_3$), 1.27 (3H, t, J = 7.0, CH_2CH_2*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.8 (C=O), 151.1 (CH=*C*), 137.9 (*C*H=C), 94.1 (*C*≡CCO), 79.0 (C≡*C*CO), 22.6 (*C*H$_2$C=C), 21.4 (C≡C*C*H$_2$CH$_2$), 21.0 (C≡CH$_2$*C*H$_2$), 13.5 (CH_3), 12.9 (CH_2*CH*$_3$), 10.4 (CH_2*CH*$_3$); LRMS m/z (%)+CI 165 (M^+, 100 %), 153 (7), 137 (12), 123 (5), 113 (22), 95 (20), 85 (6), 69 (10) and 59 (25); HRMS calcd for $C_{11}H_{16}O$ (M+H) 165.1279, found 165.1277.

Method B: To a stirred solution of 1-pentynyllithium (prepared by the dropwise addition of *n*-butyllithium (3.8 mL, 9.5 mmol, 2.5 M) to a solution of pent-1-yne (1.4 mL, 13.9 mmol) in dry tetrahydrofuran (10 mL) at – 78 ° C; and allowing it to stir for

30 min) a solution of (*E*)-2-methylpent-2-enoic acid *N*-methoxy-*N*-methyl amide (1.0 g, 6.3 mmol) in anhydrous tetrahydrofuran (5.0 mL) was added dropwise and the resultant mixture was warmed to – 3 °C over 2 h, then cooled to –78 °C and treated with glacial acetic acid (0.25 mL), then warmed to – 5 °C and poured into a mixture of ether (80 mL) and brine (80 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 80 mL). The combined organic extracts were washed with brine (2 x 80 mL), dried over anhydrous $MgSO_4$, filtred and evaporated and the residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to give **108g** (0.50 g, 50%) as a pale yellow oil. The full spectroscopic data are given above.

Oct-1-en-4-yn-3-ol (107a).[57] A solution of pent-1-yne (4.38 g, 64.3 mmol) in dry tetrahydrofuran (60 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (26.8 mL, 67 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of acrolein (3.0 g, 53.6 mmol) in dry tetrahydrofuran (20 mL). The mixture was stirred for 24 h, and then worked up as for **107g**. The oily residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to give **107a** (6.4 g, 96%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.97 (1H, m, *CH*=CH_2), 5.47 (1H, d, J = 17.0, CH=*CH*$_2$), 5.21 (1H, d, J = 10.1, CH=*CH*$_2$), 4.86 (1H, bs, *CH*OH), 2.22 (2H, t, J = 7.0, CH_2), 1.86 (1H, bs, CH*OH*), 1.58 (2H, sextet, J = 7.0, *CH*$_2$), 0.98 (3H, t, J = 7.0, *CH*$_3$); ^{13}C NMR (75 Mz, $CDCl_3$) δ_C 137.6 (*CH*=CH_2), 116.0 (CH=*CH*$_2$), 87.2 (*C*≡CCOH), 79.1 (C≡*C*COH), 63.4 (*CH*OH), 22.0 (*CH*$_2$), 20.7 (*CH*$_2$), 13.5 (*CH*$_3$).

2-Methyloct-1-en-4-yn-3-ol (107b). A solution of pent-1-yne (3.50 g, 51.4 mmol) in dry tetrahydrofuran (50 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (21.4 mL, 53.6 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of 2-methylpropenal (3.0 g, 43 mmol) in dry tetrahydrofuran (15 mL). The mixture was stirred for 3 h and then poured into saturated aqueous ammonium chloride (11.5 mL). The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (5:95 ethyl acetate: petroleum ether) to give **107b** (5.5 g, 92%) as a

pale yellow oil; IR ν_{max} (cm^{-1}) 3416 (OH), 2209 (alkyne group), 1626 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.08 (1H, s, C=C*H*H), 4.81 (1H, s, C*H*OH), 4.72 (1H, s, C=CH*H*), 2.42 (1H, bs, OH), 2.12 (2H, m, CH_2), 1.78 (3H, s, CH_3), 1.48 (2H, m, J = 7.0, CH_2CH_3), 0.92 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 143.8 (*C*=CH_2), 111.3 (C=*C*H_2), 85.7 (*C*≡CCOH), 78.5 (C≡*C*COH), 65.7 (*C*HOH), 20.4 (CH_2), 20.2 (CH_2), 18.1 (CH_3), 12.2 (CH_3); LRMS m/z (%)+CI 138 (M^+, 10 %), 123 (95), 111 (90), 95 (60), 81 (50), 67 (100), 55 (50), 53 (30); HRMS calcd for $C_9H_{14}O$ 138.1039, found 138.1039.

(*E*)-Dec-3-en-6-yn-5-ol (107c). A solution of pent-1-yne (2.9 g, 43 mmol) in dry tetrahydrofuran (50 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (17.8 mL, 44.6 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-pent-2-enal (3.0 g, 36 mmol) in dry tetrahydrofuran (5.7 mL). The mixture was stirred for 3 h, and then worked up as for **107g**. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to afford **107c** (4.0 g, 90%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3335 (OH), 2201 (alkyne group), 1620 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.91 (1H, m, *CH*=CHCOH), 5.62 (1H, dd, J = 15.3, 3.7, CH=*CH*COH), 4.83 (1H, m, *CH*OH), 2.22 (2H, t, J = 7.0, CH_2), 2.06 (2H, quintet, J = 7.0, CH_2), 1.53 (2H, sextet, J = 7.0, CH_2), 1.01 (6H, t, J = 7.0, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 135.1 (CH=*CH*COH), 128.6 (*CH*=CHCOH), 86.7 (*C*≡CCOH), 79.8 (C≡*C*COH), 63.3 (*CH*OH), 24.9 (CH_2), 22.0 (CH_2), 20.8 (CH_2), 13.5 (CH_3), 13.1 (CH_3); LRMS m/z (%)+CI 153 (M+H, 5 %), 151 (32), 135 (25), 123 (25), 85 (100), 69 (32), 67 (30), 57 (45), 55 (35); HRMS calcd for $C_{10}H_{16}O$ 153.12739 (M+H), found 153.12724.

(*E*)-1-Phenylhept-4-en-1-yn-3-ol (107d). A solution of phenylacetylene (4.37 g, 43 mmol) in dry tetrahydrofuran (50 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (17.8 mL, 45 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-pent-2-enal (3.0 g, 36 mmol) in dry tetrahydrofuran (15 mL). The mixture was stirred for 3 h, and then worked up as for **107g**. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to afford **107d** (5.6 g, 85%) as a pale yellow oil; IR

ν_{max} (cm^{-1}) 3347 (OH), 2204 (alkyne group), 1615 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.44 (2H, m, Ph), 7.32 (3H, m, Ph), 6.00 (1H, dt, J = 16.5, 7.5, *CH*=CHCOH), 5.71 (1H, dd, J = 16.5, 6.0, CH=*CH*COH), 5.08 (1H, d, J = 6.0 Hz, *CH*OH), 2.09 (2H, quintet, J = 7.5 Hz, CH_2), 1.04 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 135.8 (CH=*CH*COH), 132.1 (*ipso*-phenyl), 131.7 (phenyl), 128.8 (*para*-phenyl), 128.5 (phenyl), 127.9 (*CH*=CHCOH), 88.5 (*C*≡CCOH), 85.9 (C≡*C*COH), 63.5 (*CH*OH), 25.0 (CH_2), 13.1 (CH_3); LRMS m/z (%)+CI 187 (M+H, 20 %), 185 (45), 169 (85), 103 (100), 91 (25), 85 (90), 57 (45); HRMS calcd for $C_{13}H_{14}O$ 187.11174 (M+H), found 187.11199.

(*E*)-Non-2-en-5-yn-4-ol (107e). A solution of pent-1-yne (3.88 g, 57.0 mmol) in dry tetrahydrofuran (100 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (24 mL, 60.0 mmol, 2.5 M in hexanes). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-but-2-enal (3.0 g, 42.8 mmol) in dry tetrahydrofuran (5.7 mL). The mixture was stirred for 1 h, and then worked up as for **107g**. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to afford **107e** (5.0 g, 85%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.91 (1H, dq, J = 9.0 and 6.5, *CH*=CHOH), 5.63 (1H, dd, J = 9.0 and 6.0, C=*CH*COH), 4.80 (1H, bs, CHOH), 2.18 (2H, t, J = 7.0 Hz, CH_2), 1.84 (1H, bs, OH), 1.73 (3H, d, J = 6.5 Hz, CH=CH*CH*$_3$), 1.55 (2H, sextet, J =7.0 Hz, CH_2), 0.97 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 130.9 (CH=*CH*COH), 128.4 (*CH*=CHCOH), 86.7 (*C*≡CCOH), 79.8 (C≡*C*COH), 63.2 (CH-OH), 22.0 (CH_2), 20.7 (CH_2), 17.5 (CH_3), 13.5 (CH_3). The spectroscopic data are identical to those reported in the literature.[58]

(*E*)-1-Phenyloct-1-en-4-yn-3-ol (107f). A solution of pent-1-yne (1.72 g, 25.2 mmol) in dry tetrahydrofuran (50 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (11 mL, 27.5 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-3-phenyl-propenal (3.0 g, 22.7 mmol) in dry tetrahydrofuran (5.7 mL). The mixture was stirred for 3 h, and then worked up as for **107g**. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to afford **107f** (4.0 g, 88%) as

a pale yellow oil; IR ν_{max} (cm^{-1}) 3342 (OH), 2210 (alkyne group), 1632 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.42 (2H, m, phenyl), 7.38 (3H, m, phenyl), 6.78 (1H, d, J = 15.6 Hz, *CH*=CHCOH), 6.31 (1H, dd, J = 15.6 and 5.9 Hz, CH=*CH*COH), 5.04 (1H, m, *CH*OH), 2.24 (2H, t, J = 7.0, CH_2), 1.58 (2H, sextet, J = 7.0 Hz, CH_2), 1.03 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 136.3 (*ipso*-phenyl), 131.5 (CH=*CH*COH), 128.9 (*CH*=CHCOH), 128.6 (phenyl), 128.0 (phenyl), 127.1 (phenyl), 87.3 (*C*≡CCOH), 79.3 (C≡*C*COH), 63.2 (CHOH), 22.0 (CH_2), 20.8 (CH_2), 13.5 (CH_3); LRMS m/z (%)+CI 201 (M+H, 15%), 199 (12), 183 (90), 133 (100), 105 (12), 91 (10); HRMS calcd for $C_{14}H_{16}O$ 201.12739 (M+H), found 201.12726.

(*E*)-4-Methyl-1-phenylhept-4-en-1-yn-3-ol (107h). A solution of phenylacetylene (3.73 g, 36.5 mmol) in dry tetrahydrofuran (50 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (15.3 mL, 38.3 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-2-methylpent-2-enal (3.0 g, 30.6 mmol) in dry tetrahydrofuran (20 mL). The mixture was stirred for 3 h, and then worked up as for **107g**. The residue was purified by column chromatography (5:95 ethyl acetate: petroleum ether) to give **107h** (5.80 g, 94%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3390 (OH), 2202 (alkyne group), 1626 (C=C); ^{1}H NMR δ_H 7.45 (2H, m, phenyl), 7.30 (3H, m, phenyl), 5.67 (1H, t, J = 7.5 Hz, *CH*=C), 4.97 (1H, s, *CH*OH), 2.09 (2H, pentet, J = 7.5 Hz, CH_2CH_3), 1.60 (3H, s, CH_3), 0.90 (3H, t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR δ_C 133.3 (*ipso*-phenyl), 131.7 (phenyl), 130.2 (phenyl), 128.4 (phenyl), 128.6 (CH=*C*COH), 123.0 (*CH*=CCOH), 88.6 (*C*≡CCOH), 85.9 (C≡*C*COH), 68.6 (CHOH), 21.1 (CH_2), 13.8 (CH_3), 14.5 (CH_3); LRMS m/z (%)+EI 200 (M^+, 30%), 183 (15), 171 (90), 129 (100), 115 (30), 105 (65), 91 (22), 77 (46), 45 (45); HRMS calcd for $C_{14}H_{16}O$ 200.1201, found 200.1216.

(*E*)-1-Ethoxy-4-methylhept-4-en-1-yn-3-ol (107i).[30] A solution of ethoxy ethyne (2.0 g, 28.5 mmol, 40% w/v in hexanes) in dry tetrahydrofuran (50 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (12.0 mL, 30.0 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-2-methylpent-2-enal (2.1 g, 2.4 mL, 21.4 mmol) in dry tetrahydrofuran (15 mL). The mixture was stirred for 3 h, and then worked up as for

107g. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to give **107i** (3.23 g, 90%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.42 (1H, t, J = 7.3, CH=C), 4.64 (1H, bs, *CH*OH), 4.00 (2H, q, J = 7.0, OCH_2), 1.93 (2H, pentet, J = 7.3, CH_2CH=C), 1.61 (3H, s, CH_3), 1.25 (3H, t, J = 7.0, CH_3), 0.86 (3H, t, J = 7.3, CH_3); ^{13}C NMR δ_C (75 MHz, $CDCl_3$), 135.1 (*C*=CH), 129.3 (*CH*=C), 95.1 (C≡*C*O), 75.0 (*C*≡CO), 68.4 (COH), 38.6 (CH_2O), 21.3 (CH_2C=C), 14.7 (CH_3), 14.1 (CH_3), 12.3 (CH_3).

(*E*)-2-Methyl-1-phenyloct-1-en-4-yn-3-ol (107j). A solution of pent-1-yne (1.68 g, 24.6 mmol) in dry tetrahydrofuran (50 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (10.3 mL, 25.6 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-2-methyl-3-phenylpropenal (3.0 g, 20.5 mmol) in dry tetrahydrofuran (5.7 mL). The mixture was stirred at 25 °C for 3 h, and then worked up as for **107g**. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to give **107j** (4.0 g, 91%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3347 (OH), 2204 (alkyne group), 1618 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.31 (5H, m, Ph), 6.67 (1H, s, *CH*=C), 4.91 (1H, s, *CH*OH), 2.23 (2H, t, J = 7.0 Hz, CH_2), 1.99 (3H, s, CH_3), 1.56 (2H, sextet, J =7.0 Hz, CH_2), 1.01 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 137.9 (*C*=CH), 137.7 (*ipso*-phenyl), 129.0 (phenyl), 128.2 (phenyl), 126.3 (*CH*=C), 87.5 (*C*≡CCOH), 79.9 (C≡*C*COH), 68.3 (*CH*OH), 22.5 (CH_2), 21.4 (CH_2), 14.5 (CH_3), 13.9 (CH_3); LRMS m/z (%)+CI 215 (M+H, 30 %), 213 (35), 198 (60), 197 (100), 148 (75), 147 (99), 129 (80), 119 (85), 91 (87); HRMS calcd for $C_{15}H_{18}O$ 215.14304 (M+H), found 215.14356.

(*E*)-7-Methyldec-7-en-4-yne-1,6-diol (107k). A solution of 4-pentyn-1-ol (3.34 g, 39.8 mmol) in dry tetrahydrofuran (300 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (29.5 mL, 73.8 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-2-methylpent-2-enal (3.0 g, 30.6 mmol) in dry tetrahydrofuran (5.0 mL). The mixture was stirred at 25 °C for 20 h, and then poured into saturated aqueous ammonium carbonate (300 mL). The layers were separated and the aqueous layer was extracted

with ether (3 x 90 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (1:1 ethyl acetate: petroleum ether) to afford **107k** (2.5 g, 45%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3450 (OH), 2205 (alkyne group), 1617 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.57 (1H, t, J = 7.0 Hz, *CH*=C), 4.73 (1H, bs, *CH*OH), 3.76 (2H, t, J = 6.0 Hz, CH_2O), 2.37 (2H, t, J = 7.0 Hz, CH_2), 2.06 (2H, m, CH_2), 1.81 (2H, quintet, J = 7.0 Hz, CH_2), 1.74 (3H, s, CH_3), 0.98 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 134.4 (CH=*C*COH), 130.2 (*CH*=CCOH), 86.1 (*C*≡CCOH), 80.6 (C≡*C*COH), 68.7 (*CH*OH), 62.1 (CH_2O), 31.6 (CH_2), 21.4 (CH_2), 15.8 (CH_2), 14.2 (CH_3), 12.4 (CH_3); LRMS m/z (%)+CI 182 (M^+, 10 %), 164 (20), 153 (35), 135 (30), 121 (25), 111 (30), 97 (60), 91 (50), 83 (20), 79 (40), 69 (80), 55 (40); HRMS calcd for $C_{11}H_{18}O_2$ 182.13067, found 182.13023.

(*E*)-Methylundec-8-en-5-yne-1,7-diol (107l). A solution of 5-hexyn-1-ol (3.9 g, 39.8 mmol) in dry tetrahydrofuran (300 mL) was treated dropwise at 25 °C with a solution of butyllithium in hexanes (29.5 mL, 73.8 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min. then treated dropwise with a solution of (*E*)-2-methylpent-2-enal (3.0 g, 30.6 mmol) in dry tetrahydrofuran (5.0 mL). The mixture was stirred at 25 °C for 18 h, and then poured into saturated aqueous ammonium carbonate (300 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 90 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (1:1 ethyl acetate: petroleum ether) to afford **107l** (4.1 g, 68%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3450 (OH), 2205 (alkyne group), 1622 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.57 (1H, t, J = 7.0 Hz, *CH*=C), 4.73 (1H, s, *CH*OH), 3.68 (2H, t, J = 6.0 Hz, OCH_2), 2.29 (2H, t, J = 7.0 Hz, CH_2), 2.06 (2H, m, CH_2), 1.74 (3H, s, CH_3), 1.68 (4H, m, CH_2), 0.98 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 134.4 (CH=*C*), 130.1 (*CH*=C), 86.6 (*C*≡CCOH), 80.4 (C≡*C*COH), 68.7 (*C*HOH), 62.7 (CH_2O), 32.2 (CH_2), 25.2 (CH_2), 21.4 (CH_2), 19.0 (CH_2), 14.2 (CH_3), 12.4 (CH_3); LRMS m/z (%)+CI 195 (10 %), 179 (15), 177 (20), 99 (100), 97 (65), 95 (30), 85 (27), 81 (75), 71 (40), 69 (35), 67 (15), 59 (20), 57 (43), 55 (40); HRMS calcd for $C_{12}H_{20}O_2$ 197.15361 (M+H), found 197.15353.

(*E*)-4-Methyl-hept-4-en-1-yn-3-ol (107m).[34,59] (*E*)-2-Methylpent-2-enal (3.0 g, 30.6 mmol) was added to a solution of ethynylmagnesium bromide in THF (61.2 mL, 30.6 mmol, 0.5 M) at – 78 °C. After stirring for 2 h, the mixture was poured into a solution of saturated aqueous ammonium chloride (30 mL) and extracted with ether (2 x 30 mL). The combined organic layers were washed with water (30 mL), followed by brine (30 mL) and then dried over $MgSO_4$, and filtered. Evaporation gave **107m** (3.6 g, 95%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.61 (1H, t, J = 7.0, *CH*=C), 4.74 (1H, s, *CH*OH), 2.53 (1H, s, C≡C*H*), 2.03 (2H, pentet, J = 7.0 Hz, CH_2), 1.75 (3H, s, CH_3), 1.00 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 133.1 (CH=*C*), 130.5 (*CH*=C), 83.2 (*C*≡CH), 74.0 (C≡*C*H), 67.9 (CHOH), 21.0 (CH_2), 13.7 (CH_3), 12.0 (CH_3).

(*E*)-4-Hydroxy-5-methyloct-5-en-2-ynoic acid ethyl ester (107n). To a solution of diisopropylamine (48.0 g, 47.1 mmol) in tetrahydrofuran (100 mL), cooled to -78 °C, was added *n*-butyllithim (18.8 mL, 2.5 M solution in hexanes). After stirring for 10 min, a solution of ethyl propiolate (4.65 g, 47.1 mmol) in tetrahydrofuran (10 mL) was added over 30 min. After a further 20 min, a solution of (*E*)-2-methylpent-2-enal (3.0 g, 30.6 mmol) in tetrahydrofuran (10 mL) was added dropwise. After stirring for 20 min, the mixture was quenched by the addition of saturated aqueous ammonium chloride (30 mL), extracted with ether (3 x 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and evaporated. Purification by flash column chromatography (1:3, ethyl acetate:petroleum ether) gave **107n** as an orange oil (5.0 g, 83%); IR ν_{max} (cm^{-1}) 3362 (OH), 2201 (alkyne group), 1617 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.61 (1H, t, J = 7.0 Hz, *CH*=C), 4.85 (1H, s, *CH*OH), 4.22 (2H, q, J = 6.5 Hz, OCH_2), 2.29 (1H, bs, OH), 2.08 (2H, quintet, J = 7.0 Hz, CH_2), 1.74 (3H, s, CH_3), 1.26 (3H, t, J = 6.5 Hz, CH_3), 0.97 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.2 (C=O), 153.6 (*C*=CH), 113.8 (C=*CH*), 86.0 (C≡*C*COH), 77.0 (*C*≡CCOH), 67.8 (*CH*OH), 62.2 (CH_2O), 21.1 (CH_2), 14.0 (CH_3), 13.6 (CH_3), 12.2 (CH_3); LRMS m/z (%)+CI 196 (M^+, 50 %), 179 (82), 169 (92), 151 (40), 139 (100), 121 (65), 105 (48), 91 (70), 69 (55), 53 (60); HRMS calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1095.

2-Methylnon-2-en-5-yn-4-ol (107o). A solution of pent-1-yne (2.90 g, 42.8 mmol) in dry tetrahydrofuran (75 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (17.8 mL, 44.6 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of 3-methylbutenal (3.0 g, 35.7 mmol) in dry tetrahydrofuran (30 mL). The mixture was stirred at 25 °C for 3 h, and then worked up as for **107g**. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to give **107o** (4.0 g, 74%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3336 (OH), 2202 (alkyne group), 1622 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.35 (1H, m, *CH*=C), 5.03 (1H, m, CHOH), 2.24 (2H, t, *J* = 7.0, CH_2C≡C), 1.70 (6H, d, *J* = 6.5, CH_3), 1.52 (2H, m, CH_2), 0.97 (3H, t, *J* = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 136.5 (*C*=CH), 125.9 (C=*CH*), 85.4 (*C*≡CCOH), 81.4 (C≡*C*COH), 59.6 (*CH*OH), 22.4 (CH_2), 21.1 (CH_2), 18.4 (CH_3), 13.8 (CH_3); LRMS m/z (%)+CI 153 (M+H, 10%), 151 (15), 135 (75), 107 (25), 93 (65), 85 (100), 69 (27), 57 (30), 55 (35); HRMS calcd for $C_{10}H_{16}O$ 153.1274 (M+H), found 153.1277.

5-Methyl-1-phenylhex-4-en-1-yn-3-ol (107p). A solution of phenylacetylene (4.40 g, 42.8 mmol) in dry tetrahydrofuran (75 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (17.8 mL, 44.6 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of 3-methylbutenal (3.0 g, 35.7 mmol) in dry tetrahydrofuran (30 mL). The mixture was stirred at 25 °C for 3 h, and then worked up as for **107g**. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to give **107p** (5.0 g, 75%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3341 (OH), 2203 (alkyne group), 1630 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.43 (2H, m, phenyl), 7.30 (3H, m, phenyl), 5.47 (1H, d, *J* = 6.5, *CH*=C), 5.26 (1H, d, *J* = 6.5, *CH*OH), 1.78 (6H, s, CH_3); ^{13}C NMR (75 MHz, CDCl3) δ_C 137.6 (*C*=CH), 132.1 (phenyl), 128.7 (C=*CH*), 128.6 (phenyl), 125.1 (phenyl), 123.0 (phenyl), 90.0 (*C*≡CCOH), 84.9 (C≡*C*COH), 60.0 (CHOH), 26.0 (CH_3), 18.6 (CH_3); LRMS m/z (%)+CI 187 (M+H, 5 %), 185 (15), 171 (10), 169 (20), 151 (18), 103 (62), 85 (100), 83 (10); HRMS calcd for $C_{13}H_{14}O$ 187.11174 (M+H), found 187.11149.

1-Cyclopent-1-enyl-3-ethoxyprop-2-yn-1-ol (107q). A solution of ethoxy ethyne (2.5 g, 6.3 mL, 36.3 mmol, 40% wt. solution in hexanes) in dry tetrahydrofuran (100 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium in hexanes (15.3 mL, 38.2 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of cyclopent-1-enecarboxaldehyde (3.0 g, 27.3 mmol) in dry tetrahydrofuran (15 mL). The mixture was stirred for 3 h, and then worked up as described above. The residue was purified by column chromatography (10:90 ethyl acetate: petroleum ether) to give **107q** (2.1 g, 66%) as a pale orange oil; IR ν_{max} (cm^{-1}) 3376 (OH), 2208 (alkyne group), 1632 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.84 (1H, m, *CH*=C), 4.98 (1H, s, *CH*OH), 4.07 (2H, q, *J* = 7.0, OCH_2), 2.34 (4H, m, CH_2C=CHCH_2), 1.93 (2H, m, $CH_2CH_2CH_2$), 1.35 (3H, t, *J* = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 144.7 (*C*=CH), 126.6 (C=*CH*), 94.1 (C≡*C*O), 74.6 (*CH*OH), 61.4 (OCH_2CH_3), 38.1 (*C*≡CO), 32.2 (CH_2), 31.4 (CH_2), 23.4 (CH_2), 14.3 (CH_3); LRMS m/z (%)+CI 166 (M^+, 20 %), 137 (70), 110 (50), 95 (90), 79 (60), 67 (90), 53 (50); HRMS calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0993.

Oct-1-en-4-yn-3-one (108a). A solution of the oct-1-en-4-yn-3-ol (3.5 g, 28.2 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (39.2 g, 0.45mol) in dichloromethane (250 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108a** (2.2 g, 63%) as a yellow oil; IR ν_{max} (cm^{-1}) 2210 (alkyne group), 1685 (C=O), 1621 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.57 (1H, d, *J* = 17.3 Hz, CH=*CH*H), 6.42 (1H, dd, *J* = 10.0 and 17.3 Hz, CH=CH*H*), 6.16 (1H, d, *J* = 10.0 Hz, *CH*=CH_2), 2.42 (2H, t, *J* = 7.0 Hz, *CH_2*), 1.65 (2H, sextet, *J* = 7.0 Hz, *CH_2*), 1.06 (3H, t, *J* = 7.0 Hz, *CH_3*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.2 (C=O), 138.1 (CH_2=*CH*), 133.3 (*CH_2*=CH), 95.5 (*C*≡CC=O), 78.7 (C≡*C*C=O), 21.3 (CH_2), 20.9 (CH_2), 13.5 (CH_3); LRMS m/z (%)+CI 123 (M+H, 100 %), 111 (10), 95 (20), 71 (10), 56.9 (10), 54.9 (14); HRMS calcd for $C_8H_{10}O$ 123.0804 (M+H), found 123.0799.

2-Methyloct-1-en-4-yn-3-one (108b). A solution of the 2-methyloct-1-en-4-yn-3-ol (3.0 g, 21.7 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (30.2 g, 0.35 mol, 16 eq.) in dichloromethane (250 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108b** (2.4 g, 80%) as a yellow oil; IR ν_{max} (cm^{-1}) 2206 (alkyne group), 1683 (C=O), 1624 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.43 (1H, s, C=C*H*H), 6.00 (1H, s, C=CH*H*), 2.39 (2H, t, J = 7.0, CH_2), 1.90 (3H, s, CH_3), 1.62 (2H, m, CH_2CH_3), 1.04 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.5 (C=O), 145.5 (*C*=CH_2), 130.6 (C=*CH*$_2$), 97.4 (*C*≡CC=O), 79.2 (C≡*C*C=O), 21.9 (CH_2), 21.5 (CH_2), 13.8 (CH_3), 13.5 (CH_3);); LRMS m/z (%)+CI 137 (M+H, 100 %), 111 (15), 109 (10), 97 (12), 95 (13), 71 (10), 69 (15); HRMS calcd for $C_9H_{12}O$ 137.0961 (M+H), found 138.0965.

(*E*)-Dec-3-en-6-yn-5-one (108c). A solution of the (*E*)-dec-3-en-6-yn-5-ol (2.5 g, 16 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (12.0 g, 0.139 mol, 16 eq.) in dichloromethane (200 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108c** (2.3 g, 92%) as an orange oil; IR ν_{max} (cm^{-1}) 2203 (alkyne group), 1685 (C=O), 1622 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.24 (1H, dt, J = 15.7 and 6.5 Hz, *CH*=CHC=O), 6.16 (1H, d, J = 15.7 Hz, CH=*CH*C=O), 2.39 (4H, m, 2CH_2), 1.66 (2H, sextet, J = 7.0 Hz, CH_2CH_3) 1.11 (6H, t, J = 7.0 Hz, 2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.1 (C=O), 155.2 (CH=*CH*C=O), 131.5 (*CH*=CHC=O), 94.4 (*C*≡CC=O), 79.2 (C≡*C*C=O), 25.6 (CH_2), 21.4 (CH_2), 21.0 (CH_2), 13.6 (CH_3), 12.1 (CH_3); LRMS m/z (%)+CI 151 (M+H, 10 %), 150 (100), 149 (10), 95 (30), 83 (15), 59 (7), 57 (6); HRMS calcd for $C_{10}H_{14}O$ 151.1117 (M+H), found 151.1119.

(*E*)-1-Phenylhept-4-en-1-yn-3-one (108d). A solution of (*E*)-1-phenylhept-4-en-1-yn-3-ol (3.4 g, 18.2 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (14.5 g, 0.17 mol) in dichloromethane (200 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108d** (2.7 g, 79%) as a red oil; IR ν_{max} (cm^{-1}) 2214 (alkyne group), 1693 (C=O), 1615 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.59 (2H, m, phenyl), 7.36 (4H, m, phenyl, and *CH*=CHC=O), 6.22 (1H, d, J = 15.8 Hz, CH=*CH*C=O), 2.36 (2H, quintet, J = 7.0 Hz, CH_2), 1.14 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 178.7 (C=O), 155.6 (CH=*CH*C=O), 132.9 (*ipso*-phenyl), 132.1 (phenyl), 131.5 (*CH*=CHC=O), 130.5 (phenyl), 128.6 (phenyl), 91.1 (*C*≡CC=O), 86.3 (C≡*C*C=O), 25.8 (CH_2), 12.1 (CH_3); LRMS m/z (%)+CI 185 (M+H, 100 %), 167 (5), 145 (5), 129 (12), 103 (10); HRMS calcd for $C_{13}H_{12}O$ 185.0961 (M+H), found 185.0958.

Non-2-en-5-yn-4-one (108e). A solution of (*E*)-non-2-en-5-yn-4-ol (2.0 g, 14.5 mmol) in dichloromethane (3 mL) was added in one portion to a stirred suspension of manganese dioxide (20.2 g, 0.23 mol) in dichloromethane (200 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (5:95, ethyl acetate: hexanes) to give **108e** (1.45 g, 74 %) as a pale yellow oil; IR ν_{max} (cm^{-1}) 2212 (alkyne group), 1691 (C=O), 1620 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.14 (1H, m, *CH*=CHC=O), 6.18 (1H, d, J = 15.6 Hz, CH=*CH*C=O), 2.37 (2H, t, J = 7.0 Hz, CH_2), 1.98 (3H, d, J = 7.0 Hz, CH_3), 1.67 (2H, sextet, J = 7.0 Hz, CH_2), 1.05 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 178.8 (C=O), 149.1 (CH=*CH*C=O), 134.0 (*CH*=CHC=O), 94.4 (*C*≡CC=O), 79.1 (C≡*C*C=O), 21.4 (CH_2), 20.9 (CH_2), 18.4 (CH_3), 13.6 (CH_3); LRMS m/z (%)+CI 137 (M+H, 25 %), 121 (30), 108 (60), 95 (100), 77 (55), 69 (70); HRMS calcd for $C_9H_{12}O$ 137.0966 (M+H), found 137.0973.

(*E*)-1-Phenyloct-1-en-4-yn-3-one (108f). A solution of (*E*)-1-phenyloct-1-en-4-yn-3-ol (1.35 g, 9.0 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (11.4 g, 0.144 mol, 16 eq.) in dichloromethane (150 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108f** (1.3 g, 97%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.84 (1H, d, J = 16.1 Hz, *CH*=CHC=O), 7.56 (2H, m, phenyl), 7.42 (3H, m, phenyl), 6.80 (1H, d, J = 16.1 Hz, CH=*CH*C=O), 2.45 (2H, t, J = 7.0 Hz, CH_2), 1.72 (2H, sextet, J = 7.0 Hz, CH_2), 1.09 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.7 (C=O), 149.4 (CH=*CH*C=O), 135.5 (*ipso*-phenyl), 132.3 (*CH*=CHC=O), 130.4 (phenyl), 130.0 (phenyl), 129.9 (phenyl), 96.3 (*C*≡CC=O), 81.8 (C≡*C*C=O), 22.8 (CH_2), 22.4 (CH_2), 14.9 (CH_3). The spectroscopic data are identical to those reported in the literature.[60]

(*E*)-4-Methyl-1-phenylhept-4-en-1-yn-3-one (108h). A solution of (*E*)-4-methyl-1-phenylhept-4-en-1-yn-3-ol (4.0 g, 19.9 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (27.7 g, 0.32 mol) in dichloromethane (100 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. The mixture was worked up and purified as described for **108g** to give **108h** (3.35 g, 90%) as an orange oil; IR ν_{max} (cm^{-1}) 2202 (alkyne group), 1675 (C=O), 1624 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.60 (2H, m, phenyl), 7.40 (3H, m, phenyl), 7.24 (1H, t, J = 7.0, C*H*=C), 2.36 (2H, quintet, J = 7.0, CH_2), 1.86 (3H, s, CH_3), 1.15 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.5 (C=O), 151.8 (*CH*=C), 138.0 (CH=*C*), 132.7 (*ipso*-phenyl), 130.3 (phenyl), 128.8 (phenyl), 120.6 (phenyl), 91.0 (*C*≡CC=O), 86.1 (C≡*C*C=O), 22.8 (CH_2), 12.9 (CH_3), 10.5 (CH_3); LRMS m/z (%)+CI 199 (M^+, 100 %), 197 (20), 129 (22), 113 (15), 105 (23), 103 (15); HRMS calcd for $C_{14}H_{14}O$ (M+H) 199.1117, found 199.1115.

(*E*)-1-Ethoxy-4-methylhept-4-en-1-yn-3-one (108i). A solution of (*E*)-1-ethoxy-4-methylhept-4-en-1-yn-3-ol (1.60 g, 11.9 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (12.0 g, 0.19 mol) in dichloromethane (180 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. The mixture was worked up and purified as described for **108g** to give **108i** (1.25 g, 78%) as an orange oil; IR ν_{max} (cm^{-1}) 2215 (alkyne group), 1684 (C=O), 1627 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.86 (1H, t, J = 7.5, *CH*=C), 4.25 (2H, q, J = 7.0, OCH_2), 2.20 (2H, pentet, J = 7.5, CH_2CH=C), 1.72 (3H, s, CH_3), 1.40 (3H, t, J = 7.0, OCH_2CH_3), 1.12 (3H, t, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 181.2 (C=O), 149.4 (*C*H=C), 138.0 (CH=*C*), 102.4 (*C*≡CCO), 77.1 (OCH_2), 42.3 (C≡*C*CO), 22.9 (CH_2C=C), 14.8 (CH_3), 13.3 (CH_3), 10.9 (CH_3).

(*E*)-2-Methyl-1-phenyloct-1-en-4-yn-3-one (108j). To solution of (*E*)-2-methyl-1-phenyloct-1-en-4-yn-3-ol (3.0 g, 14.0 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (19.5 g, 0.22 mol, 16 eq.) in dichloromethane (200 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108j** (2.6 g, 87%) as a brown oil; IR ν_{max} (cm^{-1}) 2209 (alkyne group), 1686 (C=O), 1625 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.01 (1H, s, *CH*=C), 7.44 (5H, m, Ph), 2.44 (2H, t, J = 7.0 Hz, CH_2), 2.11 (3H, s, CH_3), 1.71 (2H, sextet, J = 7.0 Hz, CH_2), 1.08 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 181.4 (C=O), 145.5 (*CH*=C), 138.5 (*C*=CH), 136.0 (*ipso*-phenyl), 130.0 (phenyl), 129.5 (*para*-phenyl), 128.4 (phenyl), 95.6 (*C*≡CC=O), 79.4 (C≡*C*C=O), 21.5 (CH_2), 21.2 (CH_2), 14.0 (CH_3), 12.6 (CH_3); LRMS m/z (%)+CI 214 (M+H, 60 %), 213 (100), 212 (15), 183 (15), 145 (50), 95 (47); HRMS calcd for $C_{15}H_{16}O$ 213.1274 (M+H), found 213.1272.

(*E*)-10-Hydroxy-4-methyldec-3-en-6-yn-5-one (108k). A solution of (*E*)-7-methyldec-7-en-4-yne-1,6-diol (3.0 g, 16.5 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (22.9 g, 0.263 mol, 16 eq.) in dichloromethane (250 mL) under an atmosphere of nitrogen. Stirring

was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (1:1 ethyl acetate: hexanes) to give **108k** (2.4 g, 84%) as a colourless oil; IR ν_{max} (cm^{-1}) 3495 (OH), 2205 (alkyne group), 1678 (C=O), 1620 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.08 (1H, t, J = 7.0, *CH*=C), 3.77 (2H, t, J = 6.0, OCH_2), 2.54 (2H, t, J = 7.0, CH_2), 2.28 (2H, m, CH_2), 1.89 (2H, m, CH_2), 1.78 (3H, s, CH_3), 0.85 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 181.1 (C=O), 151.9 (*CH*=C), 138.1 (CH=*C*), 93.8 (*C*≡CCO), 84.2 (C≡*C*CO), 61.6 (OCH_2), 34.5 (CH_2), 22.4 (CH_2), 21.4 (CH_2), 16.0 (CH_3), 15.4 (CH_3); LRMS m/z (%)+CI 181 (M+H, 100 %), 179 (25), 167 (15), 163 (23), 151 (15), 113 (20), 111 (22), 99 (15), 97 (40), 87 (15), 84.9 (25), 83 (10); HRMS calcd for $C_{11}H_{16}O_2$ 181.1223 (M+H), found 181.1220

(*E*)-11-Hydroxy-4-methylundec-3-en-6-yn-5-one (108l). A solution of (*E*)-methylundec-8-en-5-yne-1,7-diol (2.0 g, 10.2 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (14.2 g, 0.163 mol, 16 eq.) in dichloromethane (180 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (1:1, ethyl acetate: hexanes) to give **108l** (1.8 g, 90%) as a colourless oil; IR ν_{max} (cm^{-1}) 3510 (OH), 2208 (alkyne group), 1680 (C=O), 1618 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.10 (1H, t, J = 7.0 Hz, *CH*=C), 3.65 (2H, t, J = 6.0 Hz, OCH_2), 2.97 (1H, bs, OH), 2.46 (2H, t, J = 7.0 Hz, CH_2), 2.28 (2H, quintet, J = 7.0 Hz CH_2), 1.78 (3H, s, CH_3), 1.73 (4H, m, CH_2), 1.11 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 181.2 (C=O), 152.1 (*CH*=C), 138.0 (CH=*C*), 94.6 (*C*≡CC=O), 79.2 (C≡*C*C=O), 61.8 (CH_2O), 32.0 (CH_2), 24.8 (CH_2), 23.0 (CH_2), 18.5 (CH_2), 13.1 (CH_3), 10.9 (CH_3); LRMS m/z (%)+CI 195 (M+H, 100 %), 177 (15), 165 (5), 149 (6), 125 (6), 109 (8), 97 (72), 69 (5); HRMS calcd for $C_{12}H_{18}O_2$ 195.1380 (M+H), found 195.1373.

(*E*)-4-Methylhept-4-en-1-yn-3-one (108m). A solution of (*E*)-4-methyl-hept-4-en-1-yn-3-ol (3.0 g, 24.2 mmol) in dichloromethane (3 mL) was added in one portion to a stirred suspension of manganese dioxide (33.6 g, 0.39 mol, 16 eq.) in dichloromethane (250 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (silica gel, 10:90, ethyl acetate: hexanes) to give **108m** (2.2 g, 73%) as an orange oil; IR ν_{max} (cm^{-1}) 2213 (alkyne group), 1696 (C=O), 1612 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.18 (1H, t, J = 7.0 Hz, C*H*=C), 3.14 (1H, s, C≡C*H*), 2.30 (2H, quintet, J = 7.0 Hz, CH_2), 1.79 (3H, s, CH_3), 1.12 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.7 (C=O), 153.2 (*C*H=C), 137.6 (CH=*C*), 79.7 (*C*≡CH), 79.0 (C≡*C*H), 22.8 (CH_2), 12.8 (CH_3), 10.2 (CH_3); LRMS m/z (%)+CI 121 (M^+, 20 %), 107 (15), 97 (42), 77 (20), 69 (36), 53 (25); HRMS calcd for $C_8H_{10}O$ 122.0732, found 122.0728.

(*E*)-5-Methyl-4-oxo-oct-5-en-2-ynoic acid ethyl ester (108n). A solution of (*E*)-4-hydroxy-5-methyloct-5-en-2-ynoic acid ethyl ester (4.0 g, 20.4 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (28.0 g, 0.326 mol, 16 eq.) in dichloromethane (300 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108n** as an orange oil (3.35 g, 85%); IR ν_{max} (cm^{-1}) 2209 (alkyne group), 1690 (C=O), 1621 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.13 (1H, t, J = 7.5 Hz, *CH*=C), 4.29 (2H, q, J = 7.0 Hz, OCH_2), 2.35 (2H, quintet, J = 7.5 Hz, CH_2), 1.81 (3H, s, CH_3), 1.34 (3H, t, J = 7.0 Hz, CH_3), 1.13 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 178.3 (C=O), 154.8 (*CH*=C), 152.5 (*C*=*O*), 137.7 (CH=*C*), 79.7 (*C*≡CC=O), 79.5 (C≡*CC*=*O*), 62.8 (OCH_2), 23.0 (CH_2), 14.0 (CH_3), 12.7 (CH_3), 10.2 (CH_3); LRMS m/z (%)+CI 195 (M^+, 45 %), 165 (30), 149 (80), 120 (70), 107 (40), 97 (75), 91 (62), 79 (32), 69 (100), 57 (28); HRMS calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0950.

2-Methylnon-2-en-5-yn-4-one (108o). A solution of 2-methylnon-2-en-5-yn-4-ol (3.0 g, 19.7 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (27.4 g, 0.315 mol) in dichloromethane (200 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **108o** (2.1 g, 71%) as a colourless oil; IR ν_{max} (cm^{-1}) 2205 (alkyne group), 1672 (C=O), 1626 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.14 (1H, s, *CH*=C), 2.35 (2H, t, J = 6.5, CH_2), 2.21 (3H, s, CH_3), 1.92 (3H, s, CH_3), 1.62 (2H, m, CH_2), 1.02 (3H, t, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 177.3 (C=O), 157.6 (*C*=CH), 126.6 (C=*CH*), 92.9 (*C*≡CCO), 83.8 (C≡*C*CO), 28.1 (2 x CH_3), 21.4 (CH_2), 21.4 (CH_2), 13.9 (CH_3); LRMS m/z (%)+CI 151 (M+H, 100 %), 135 (5), 111 (6), 95 (20), 83 (17), 57 (10); HRMS calcd for $C_{10}H_{14}O$ 151.1117 (M+H), found 151.1114.

5-Methyl-1-phenylhex-4-en-1-yn-3-one (108p). A solution of 5-methyl-1-phenylhex-4-en-1-yn-3-ol (3.0 g, 16.1 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (22.4 g, 0.26 mol) in dichloromethane (200 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. Then the mixture was filtered through celite, and the celite thoroughly washed with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (silica gel, 10:90, ethyl acetate: hexanes) to give **108p** (2.2 g, 74%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.56-7.30 (5H, m, Ph), 6.30 (1H, s, *CH*=C), 2.42 (3H, s, CH_3), 1.97 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.9 (*C*=O), 158.5 (*C*=CH), 133.6 (phenyl), 130.7 (C=*CH*), 128.7 (phenyl), 126.6 (phenyl), 120.9 (phenyl), 90.7 (*C*≡CCO), 89.5 (C≡*C*CO), 28.3 (CH_3), 21.6, (CH_3). The spectroscopic data are identical to those reported in the literature.[61]

1-Cyclopent-1-enyl-3-ethoxy-propynone (108q). A solution of 1-cyclopent-1-enyl-3-ethoxyprop-2-yn-1-ol (2.0 g, 12.0 mmol) in dichloromethane (2 mL) was added in one portion to a stirred suspension of manganese dioxide (30.0 g, 0.345 mol) in dichloromethane (250 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h. The mixture was worked up and purified as described for **108g** to give **108q** (1.60 g, 80%) as an orange oil; IR ν_{max} (cm^{-1}) 2216 (alkyne group), 1680 (C=O), 1624 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.01 (1H, s, *CH*=C), 4.28 (2H, q, J = 7.5, OCH_2), 2.56 (4H, t, J = 7.5, $CH_2CH_2CH_2$), 1.94 (2H, pentet, J = 7.5, $CH_2CH_2CH_2$), 1.45 (3H, t, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.2 (C=O), 147.4 (CH=*C*CO), 125.2 (*CH*=CCO), 101.3 (*C*≡CCO), 71.3 (CH_2O), 33.7 (CH_2), 42.9 (C≡*C*CO), 30.8 (CH_2), 23.2 (CH_2), 14.4 (CH_3); LRMS m/z (%)+CI 165 (M^+, 60 %), 153 (68), 137 (100), 111 (32), 95 (80), 85 (42), 71 (25), 55 (15); HRMS calcd for $C_{10}H_{12}O_2$ (M+H) 165.0915, found 165.0913.

(*R*)-1,2–Dihydroxy-2-methyloct-4-yn-3-one (109b). To a stirred solution of modified ADmix-α (6.2 g, containing an additional 16.0 mg of potassium osmate) in 1:1 *tert*-butyl alcohol-water (35 mL) was added sodium hydrogen carbonate (1.11 g, 13.2 mmol) at 0 °C. A solution of 2-methyloct-1-en-4-yn-3-one (0.60 g, 4.41 mmol) in toluene (3 mL) was added and the mixture was stirred until the reaction was complete as determined by TLC (~ 24 h). Ethyl acetate (20 mL) was added followed by sodium metabisulfite (6.6 g) and the solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (4 x 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (2 x 15 mL, 1 M) then dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (30:70 ethyl acetate: petroleum ether) to give **109b** (0.60 g, 81%) as an orange oil; $[\alpha]_D$ = + 80.8 (c 0.08, $CHCl_3$); IR ν_{max} (cm^{-1}) 3446 (OH), 2212 (alkyne group), 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.95 (1H, d, J = 11.5, C*H*HOH), 3.60 (1H, d, J = 11.5, CH*H*OH), 2.36 (2H, t, J = 7.0, CH_2), 1.62 (2H, m, CH_2CH_3), 1.35 (3H, s, CH_3), 0.97 (3H, t, J = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 190.5 (C=O), 101.3 (*C*≡CC=O), 80.8 (C≡*C*C=O), 67.8 (CH_2OH), 21.4 (CH_2), 21.2 (CH_2), 21.1 (CH_3), 13.5 (CH_3); LRMS m/z (%)+CI 171 (M^+, 25 %), 153 (30), 141 (100), 137 (50), 123 (55), 111 (30), 99 (40), 97 (45), 95 (45), 85 (30), 71 (35), 37 (25); HRMS calcd for $C_9H_{14}O_3$ (M+H) 171.1016, found 171.1015.

(*3S,4R*)-3,4-Dihydroxy-dec-6-yn-5-one (109c). To a stirred solution of modified ADmix-α (3.5 g, containing an additional 9.0 mg of potassium osmate) in 1:1 *tert*-butyl alcohol-water (24 mL) was added sodium hydrogen carbonate (0.63 g, 7.5 mmol) and methanesulfonamide (0.24 g, 2.5 mmol) at 0 °C. A solution of (*E*)-dec-3-en-6-yn-5-one (0.40 g, 2.5 mmol) in toluene (3 mL) was added and the mixture was stirred until the reaction was complete as determined by TLC (~ 24 h). Ethyl acetate (20 mL) was added followed by sodium metabisulfite (6.5 g) and the solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (2 x 35 mL, 1M) then dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (30:70 ethyl acetate: petroleum ether) gave **109c** (0.12 g, 50%) as an orange oil; IR ν_{max} (cm^{-1}) 3512 (OH), 2217 (alkyne group), 1697 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.17 (1H, s, *CH*OH), 4.12 (1H, t, *J* = 4.0, *CH*OH), 2.43 (2H, t, *J* = 7.0, C≡C*CH*$_2$), 1.66 (4H, m, *CH*$_2$), 1.04 (6H, t, *J* = 7.0, *CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 187.9 (C=O), 103.9 (*C*≡CCO), 80.1 (CHOH), 78.0 (C≡*C*CO), 73.4 (CHOH), 27.5 (*CH*$_2$), 21.2 (2*CH*$_2$), 13.5 (*CH*$_3$), 10.3 (*CH*$_3$).

(*4R,5S*)-4,5-dihydroxy-1-phenyl-hept-1-yn-3-one (109d). To a stirred solution of modified ADmix-α (2.8 g, containing an additional 8.1 mg of potassium osmate) in 1:1 *tert*-butyl alcohol-water (20 mL) was added sodium hydrogen carbonate (0.55 g, 6.5 mmol) and methanesulfonamide (0.21 g, 2.17 mmol) at 0 °C. A solution of (*E*)-1-phenylhept-4-en-1-yn-3-one (0.40 g, 2.17 mmol) in toluene (3 mL) was added and the mixture was stirred until the reaction was complete as determined by TLC (~ 24 h). Ethyl acetate (20 mL) was added followed by sodium metabisulfite (1.5 g) and the solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (2 x 35 mL, 1 M) then dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (30:70 ethyl acetate: petroleum ether) gave **109d** (0.22 g, 47%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 3502 (OH), 2209 (alkyne group), 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.60 (2H, m, phenyl), 7.40 (3H, m, phenyl), 4.32 (1H, m, *CH*OH), 4.22 (1H, t, *J* = 6.0 Hz, *CH*OH), 1.76 (2H, quintet, *J* = 7.5 Hz, CH_2), 1.08 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}C NMR

(75 MHz, $CDCl_3$) δ_C 187.7 (C=O), 133.2 (*ipso*-phenyl), 131.4 (phenyl), 128.8 (phenyl), 119.3 (phenyl), 96.9 (*C*≡CC=O), 85.0 (C≡*C*C=O), 80.2 (O=C*C*HOH), 73.5 (*C*HOH), 27.5 (CH_2), 10.3 (CH_3).

(*2S,3R*)-2,3-Dihydroxy-non-5-yn-4-one (109e). To a stirred solution of modified ADmix-α (6.20 g, containing an additional 16.0 mg of potassium osmate and also an additional 0.71 g of the chiral ligand, $(DHQ)_2$-PHAL)) in 1:1 *tert*-butyl alcohol-water (40 mL) at 0 °C was added sodium hydrogen carbonate (1.11 g, 13.2 mmol) and methanesulfonamide (0.42 g, 4.40 mmol). A solution of the non-2-en-5-yn-4-one (0.60 g, 4.40 mmol) in toluene (2 mL) was added and the mixture was stirred until it was complete as determined by TLC (~ 24 h). Ethyl acetate (20 mL) was added followed by sodium metabisulfite (6.6 g) and the solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (2 x 35 mL, 1M) then dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (60:40 ethyl acetate: petroleum ether) gave **109e** (0.40 g, 53%) as an orange oil; IR ν_{max} (cm^{-1}) 3430 (OH), 2203 (alkyne group), 1693 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.10 (1H, quintet, J = 6.0, CHOH), 3.93 (1H, m, CHOH), 2.38 (2H, t, J = 7.0, CH_2), 1.62 (2H, m, CH_2), 1.23 (3H, d, J = 6.0, CH_3), 1.03 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 179.5 (C=O), 94.9 (*C*≡CCO), 79.2 (C≡*C*CO), 67.9 (CHOH), 67.2 (CHOH), 34.0 (CH_2), 27.5 (CH_2), 21.0 (CH_3), 13.6 (CH_3); LRMS m/z (%)+CI 171 (M+H, 50 %), 163 (30), 153 (100), 127 (95), 109 (40), 93 (98), 81 (40), 71 (20); HRMS calcd for $C_9H_{14}O_3$ 171.1021 (M+H), found 171.1024.

(*3S,4R*)-3,4-Dihydroxy-4-methyl-dec-6-yn-5-one (109g). To a stirred solution of modified ADmix-α (6.1 g, containing an additional 22.0 mg of potassium osmate) in 1:1 *tert*-butyl alcohol-water (60 mL) was added sodium hydrogen carbonate (1.54 g, 18.3 mmol) and methanesulfonamide (0.58 g, 6.1 mmol) at 0 °C. A solution of (*E*)-4-methyldec-3-en-6-yn-5-one (1.0 g, 6.1 mmol) in toluene (2 mL) was added and the mixture was stirred until the reaction was complete as determined by TLC (~ 24 h). Ethyl acetate (30 mL) was added followed by sodium metabisulfite (12 g) and the

solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers were washed with aqueous sodium hydroxide (2 x 30 mL, 1 M) then dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (1:5 ethyl acetate: petroleum ether) gave **109g** (1.14 g, 95%) as an orange oil; $[\alpha]_D$ = + 90.7 (c 0.03 in $CHCl_3$); IR ν_{max} (cm^{-1}) 3394 (OH), 2212 (alkyne group), 1690 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.95 (1H, dt, *J* = 10.0, 2.5, C*H*OH), 2.50 (2H, t, *J* = 7.0, C≡CC*H*$_2$), 1.74 (4H, m, 2C*H*$_2$CH$_3$), 1.43 (3H, s, CH_3), 1.15 (3H, t, *J* = 7.5, CH_3), 1.14 (3H, t, *J* = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 191.6 (C=O), 101.3 (*C*≡CC=O), 82.6 (C≡*C*C=O), 78.1 (O=C*C*OH), 76.5 (COH), 24.0 (CH_2), 21.7 (CH_2), 21.6 (CH_2), 21.5 (CH_3), 13.8 (CH_3), 10.7 (CH_3); LRMS m/z (%)+FAB 199 (M+, 60), 181 (10), 154 (32), 141 (100), 107 (15), 95 (40), 69 (17), 57 (30), 43 (55); HRMS calcd for $C_{11}H_{18}O_3$ (M+H) 199.1334, found 199.1330.

(*4R,5S*)-4,5-Dihydroxy-4-methyl-1-phenylhept-1-yn-3-one (109h). To a stirred solution of modified ADmix-α (5.0 g, containing an additional 18.0 mg of potassium osmate) in 1:1 *tert*-butyl alcohol-water (50 mL) was added sodium hydrogen carbonate (1.28 g, 15.2 mmol) and methanesulfonamide (0.48 g, 5.05 mmol) at 0 °C. A solution of (*E*)-4-methyl-1-phenylhept-4-en-1-yn-3-one (1.0 g, 5.05 mmol) in toluene (3 mL) was added and the mixture was stirred until the reaction was complete as determined by TLC (~ 24 h). Ethyl acetate (20 mL) was added followed by sodium metabisulfite (6.5 g) and the solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (2 x 35 mL, 1 M) then dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (30:70 ethyl acetate: petroleum ether) gave **109h** (0.77 g, 66%); as an orange oil; $[\alpha]_D$ = + 1.69 (c 0.59, $CHCl_3$); IR ν_{max} (cm^{-1}) 3429 (OH), 2202 (alkyne group), 1685 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.60 (2H, m, phenyl), 7.42 (3H, m, phenyl), 3.96 (2H, bs, 2OH), 2.34 (1H, bs, *CH*OH), 1.74-1.53 (2H, m, CH_2), 1.43 (3H, s, CH_3), 1.06 (3H, t, *J* = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 192.9 (C=O), 133.1 (*ipso*-phenyl), 131.2 (phenyl), 129.4 (phenyl), 119.8 (phenyl), 97.3 (*C*≡CC=O), 84.8 (C≡*C*C=O), 82.6 (COH), 77.7 (*CH*OH), 24.1 (CH_2), 21.9 (CH_3),

10.8 (CH_3); LRMS m/z (%)+CI 233 (M+H, 56%), 203 (47), 173 (85), 147 (66), (90), 120 (63), 103 (100), 91 (39); HRMS calcd for $C_{14}H_{16}O_3$ 232.1099, found 232.1103.

4,5-Dihydroxy-4-methyl-1-phenylhept-1-yn-3-one (*rac*-109h). (*E*)-4-methyl-1-phenylhept-4-en-1-yn-3-one (**1c**) (1.0 g, 5.05 mmol) and citric acid (0.79 g, 3.77 mmol) were dissolved in a 1:1 mixture of *tert*-butyl alcohol-water (5 mL) in a 25 mL Erlenmeyer flask. Potassium osmate (1.85 mg, 5.02 x 10^{-5} mol) was then added followed by 4-methylmorpholine *N*-oxide (0.75 g, 5.53 mmol). The bright green mixture was stirred at 20 °C for 24 h, by which time it had become nearly colourless. The *tert*-butyl alcohol was removed on a rotary evaporator, and the aqueous residue was acidified with hydrochloric acid (1mL, 1M) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give racemic **109h** (0.59 g, 50%) as an orange oil. Spectroscopic data were identical to those given for enantiopure **109h** prepared above.

***N*-Methoxy-*N*-methyl-3-phenylacrylamide (116).**[62] Isobutyl chloroformate (5.54 g, 40.5 mmol) was added to a solution of cinnamic acid (6.0 g, 40.5 mmol) and 4-methylmorpholine (8.20 g, 81.1 mmol) in anhydrous dichloromethane (200 mL) at 0 °C. After stirring for 20 min, *N,O*-dimethylhydroxylamine hydrochloride (3.95 g, 40.5 mmol) was added and the resulting solution was stirred at 0 °C for 20 min and at 20 °C for 2 h. The mixture was partitioned between water (100 mL) and dichloromethane (2 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel, 30:70, ethyl acetate: petroleum ether) to give **116** (5.0 g, 64%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.82 (1H, d, J = 16.0, C*H*=CHCO), 7.56 (2H, m, phenyl), 7.40 (3H, m, phenyl), 7.06 (1H, d, J = 16.0, CH=C*H*CO), 3.76 (3H, s, OCH_3), 3.31 (3H, s, NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.0 (C=O), 143.5 (*CH*=CHCO), 135.2 (*ipso*-phenyl), 129.9 (phenyl), 128.8 (phenyl), 128.1 (phenyl), 115.8 (CH=*CH*CO), 61.9 (OCH_3), 32.5 (NCH_3).

(*2S,3R*)-2,3-Dihydroxy-*N*-methoxy-*N*-methyl-3-phenylpropionamide (117).[37] To a stirred solution of modified ADmix-β (14.7 g, containing an additional 38.2 mg of potassium osmate, plus an additional 0.41 g of the chiral ligand $(DHQD)_2PHAL$) in

1:1 *tert*-butyl alcohol-water (60 mL) at 0 °C was added *N*-methoxy-*N*-methyl-3-phenylacrylamide (2.0 g, 10.5 mmol) and the mixture was stirred until the reaction was complete as determined by TLC (~ 24 h). Ethyl acetate (30 mL) was added followed by sodium metabisulfite (21.0 g) and the solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (100% ethyl acetate) gave **117** (1.5 g, 63%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.37 (5H, m, phenyl), 4.97 (1H, s, CHOH), 4.60 (1H, s, CHOH), 3.64 (3H, s, OCH_3), 3.26 (3H, s, NCH_3), 3.03 (1H, bs, OH), 1.60 (1H, bs, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.5 (C=O), 137.2 (*ipso*-phenyl), 28.4 (phenyl), 127.9 (phenyl), 126.1 (phenyl), 74.8 (COH), 72.3 (COH), 61.2 (OCH_3), 32.5 (NCH_3).

(*4S,5R*)-2,2-Dimethyl-5-phenyl-[1,3]dioxolane-4-carboxylic acid *N*-methoxy-*N*-methyl amide (118). A solution of (*2R,3S*)-2,3-dihydroxy-*N*-methoxy-*N*-methyl-3-phenylpropionamide (1.50 g, 6.67 mmol) in a 1:1 mixture of *N,N*-dimethylformamide: 2,2-dimethoxypropane (89 mL) at 20 °C was treated with *p*-toluenesulfonic acid monohydrate (0.30 g). After 24 h saturated aqueous sodium hydrogen carbonate (25 mL), water (25 mL) and diethyl ether (25 mL) were added to the mixture, and the aqueous layer was separated and extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with water (25 mL) and brine (25 mL) and then dried ($MgSO_4$). Filtration and evaporation gave a residue that was purified by flash column chromatography (20:80, ethyl acetate: petroleum ether) to afford **118** (1.0 g, 79%) as a pale yellow oil; $[\alpha]_D$ = + 47.8 (c 0.03, $CHCl_3$); IR (cm^{-1}) ν_{max} 1715 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.44 (2H, m, phenyl), 7.35 (3H, m, phenyl), 5.39 (1H, d, *J* = 7.5, O*CH*CO), 4.68 (1H, d, *J* = 7.5, OCH), 3.48 (3H, s, OCH_3), 3.18 (3H, s, NCH_3), 1.61 (3H, s, CH_3CCH_3), 1.57 (3H, s, CH_3CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.0 (C=O), 137.7 (*ipso*-phenyl), 128.5 (phenyl), 128.4 (phenyl), 126.8 (phenyl), 111.1 ($C(CH_3)_2$), 80.3 (*OCH*), 78.8 (*OCH*), 61.5 (OCH_3), 32.4 (NCH_3), 27.1 (CH_3), 26.2 (CH_3).

1-((*4S,5R*)-2,2-Dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-hex-2-yn-1-one (119). A solution of pent-1-yne (0.42 g, 6.2 mmol) in dry tetrahydrofuran (25 mL) was treated

dropwise at 20 °C with a solution of *n*-butyllithium in hexanes (2.0 mL, 4.9 mmol, 2.5 M). The mixture was stirred at 20 °C for 30 min and then added slowly to a stirred solution of 2,2-dimethyl-5-phenyl-[1,3]dioxolane-4-carboxylic acid *N*-methoxy-*N*- methyl amide (0.80 g, 3.1 mmol) in tetrahydrofuran (20 mL). This mixture was stirred at 20 °C for 1 h and then poured into saturated aqueous ammonium carbonate (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel (10:90 ethyl acetate: petroleum ether) to give **119** (0.90 g, 85%) as a pale yellow oil; $[\alpha]_D$ = + 53.7 (c 0.24 in $CHCl_3$); IR ν_{max} (cm^{-1}) 2206 (alkyne group), 1703 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.35 (5H, m, phenyl), 5.14 (1H, d, *J* = 7.6, OCH), 4.38 (1H, d, *J* = 7.6, OCH), 2.33 (2H, t, *J* = 7.0, $CH_2CH_2CH_3$), 1.62 (3H, s, $OCCH_3CH_3$), 1.56 (3H, s, $OCCH_3CH_3$), 1.55 (2H, m, CH_2CH_3) 0.96 (3H, t, *J* = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 185.2 (C=O), 137.6 (*ipso*-phenyl), 128.6 (phenyl), 126.8 (phenyl), 111.8 ($C(CH_3)_2$), 88.0 (OCHCO), 87.5 (C≡CCO), 80.3 (OCH), 79.3 (C≡CCO), 27.1 (CH_2), 26.1 (CH_2), 21.1 (CH_3), 21.0 (CH_3), 13.5 (CH_3); LRMS m/z (%)+FAB 295 (M^+, 30 %), 218 (5), 198 (20), 176 (100), 172 (27); HRMS calcd for $C_{17}H_{20}O_3$ (M+Na) 295.1310, found 295.1328.

(*S*)-2-((*R*)-Hydroxyl-phenyl-methyl)-5-propyl-furan-3-one (110f). To a stirred solution of 1-((*4R,5S*)-2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-hex-2-yn-1-one (0.50 g, 1.75 mmol) in acetone (30 mL, HPLC grade) at 20 °C was added acidified mercury(II) sulfate solution (0.30 mL, 0.1 M obtained by dissolving yellow mercury(II) oxide in aqueous 2.5% H_2SO_4). The mixture was stirred for 30 min then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was taken up in ether (20 mL) and the solution was washed with water (20 mL). The aqueous layer was extracted with ether (2 x 20 mL), and the combined extracts washed with saturated aqueous sodium hydrogen carbonate (30 mL) then brine (30 mL), and dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography (30:70 ethyl acetate: petroleum ether) to give **110f** (0.20 g, 50%) as a yellow oil; $[\alpha]_D$ = + 90.7 (c 0.08, $CHCl_3$); IR ν_{max} (cm^{-1}) 3405

(OH), 1684 (C=O), 1647 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.35 (5H, m, phenyl), 5.42 (1H, s, *CH*=C), 4.67 (2H, d, J = 3.5, C*H*OH), 3.04 (1H, bs, CHO*H*), 2.44 (2H, t, J = 6.0, CH_2), 1.60 (2H, m, CH_2CH_3), 0.95 (3H, t, J = 7.4, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 203.5 (C=O), 195.7 (*C*=CCO), 139.0 (*ipso*-phenyl), 128.9 (phenyl), 128.3 (phenyl), 126.5 (phenyl), 104.8 (*C*H=C), 86.6 (OCH), 72.8 (CHOH), 32.7 (CH_2), 19.5 (CH_2), 13.6 (CH_3); LRMS m/z (%)+CI 233 (M^+, 70 %), 215 (72), 187 (20), 167 (25), 155 (60), 141 (20), 127 (100); HRMS calcd for $C_{14}H_{16}O_3$ (M+H) 233.1178, found 233.1179.

Enantiomeric excess of **110f** was determined by HPLC analysis using a Chiralcel OD column (10:90 isopropanol: *n*-hexane, λ=210 nM), the major enantiomer eluting after 15.76 min and the minor enantiomer after 14.21 min, (flow rate of 0.7 mL/min)

(*R*)-5-Ethoxy-2-((*S*)-1-hydroxypropyl)-2-methylfuran-3-one (110i). To a stirred solution of modified ADmix-α (6.63 g, containing an additional 22.0 mg of potassium osmate) in 1:1 *tert*-butyl alcohol-water (50 mL) was added sodium hydrogen carbonate (1.52 g, 18.1 mmol) and methanesulfonamide (0.57 g, 6.0 mmol) at 0 °C. A solution of (*E*)-1-ethoxy-4-methylhept-4-en-1-yn-3-one (1.0 g, 6.0 mmol) in toluene (3 mL) was added and the mixture was stirred until it was complete as determined by TLC (~ 24 h). Ethyl acetate (20 mL) was added followed by sodium metabisulfite (6.5 g) and the solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (2 x 35 mL, 1 M) then dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (50:50 ethyl acetate: petroleum ether) to give **110i** (0.59 g, 50%) as an orange oil; $[\alpha]_D$ = + 60.0 (c 0.05 in $CHCl_3$); IR ν_{max} (cm^{-1}) 3426 (OH), 1695 (C=O), 1644 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.74 (1H, s, *CH*=C), 4.24 (2H, q, J = 7.0, OCH_2), 3.69 (1H, dt, J = 5.3 and 2.6, C*H*OH), 1.70 (1H, m, C*H*HCHOH), 1.46 (3H, t, J = 7.0, OCH_2CH_3), 1.43 (3H, s, CCH_3), 1.37 (1H, m, CH*H*CHOH), 1.06 (3H, t, J = 7.0, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 202.2 (C=O), 184.3 (*C*=CHCO), 93.7 (CH_3CO), 80.1 (*C*H=C), 75.4 (*CH*OH), 68.2 (CH_2O), 23.9 (CH_2CH_3), 19.1 (CH_3), 14.5 (CH_3), 10.8 (CH_3); LRMS m/z (%)+CI 201 (M+,

15 %), 143 (100), 115 (70), 59 (75); HRMS calcd for $C_{10}H_{16}O_4$ (M+H) 201.1121, found 201.1121.

Enantiomeric excess of **110i** was determined by HPLC analysis using a Chiralcel OD column (10:90 isopropanol: *n*-hexane, λ=210 nM), the major enantiomer eluting after 16.02 min and the minor enantiomer after 14.42 min (flow rate of 0.7 mL/min).

Cyclopent-1-enecarboxaldehyde (122).[39] A solution of sodium metaperiodate (13.6 g, 6.63 mmol) in water (165 mL) was treated with *trans*-cyclohexane-1,2-diol (6.0 g, 51.7 mmol). The mixture was stirred for 30 min and then treated with 20% aqueous potassium hydroxide (19 mL) and ether (22 mL). The resulting mixture was stirred vigorously for 10 min; the organic layer was separated and the aqueous layer was extracted with ether (4 x 55 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give **122** (3.8 g, 67%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.75 (1H, s, CH=O), 6.83 (1H, m, CH=C), 2.55 (2H, m, CH_2), 2.51 (2H, m, CH_2), 1.96 (2H, t, J = 7.5, CH_2C=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 189.8 (*C*H=O), 152.9 (*CH*=C), 147.9 (CH=*C*), 33.6 (CH_2) 28.3 (CH_2), 22.9 (CH_2).

(*5R,6S*)-2-Ethoxy-6-hydroxy-1-oxaspiro[4.4]non-2-en-4-one (110q). To a stirred solution of modified ADmix-α (4.2 g, containing an additional 11.0 mg of potassium osmate) in 1:1 *tert*-butyl alcohol-water (32 mL) was added sodium hydrogen carbonate (0.76 g, 9.0 mmol) and methanesulfonamide (0.29 g, 3.0 mmol) at 0 °C. A solution of 1-cyclopent-1-enyl-3-ethoxypropynone (0.50 g, 3.0 mmol) in toluene (3 mL) was added and the mixture was stirred until the reaction was complete as determined by TLC (~ 24 h). Ethyl acetate (16 mL) was added followed by sodium metabisulfite (4.5 g) and the solution was allowed to warm to 20 °C with stirring. The aqueous layer was separated and extracted with ethyl acetate (4 x 20 mL); the combined organic layers were washed with aqueous sodium hydroxide (10 mL, 1M), dried (Na_2SO_4) and then filtered. Evaporation gave a residue that was purified by flash column chromatography (30:70 ethyl acetate: petroleum ether) to give **110q** (0.37 g, 62%) as an orange oil; $[\alpha]_D$ = + 30.2 (c 0.04 in $CHCl_3$); IR ν_{max} (cm^{-1}) 3408 (OH), 1693 (C=O), 1645 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.76 (1H, s,

C*H*=C), 4.25 (3H, m, C*H*OH and OCH_2), 2.13 (2H, m, CH_2), 1.91-1.71 (4H, m, $2CH_2$), 1.42 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 199.6 (C=O), 183.7 (*C*=CH), 98.4 (O*C*CO), 80.7 (C=*C*H), 76.8 (*C*HOH), 68.0 (OCH_2), 32.1 (CH_2), 31.8 (CH_2), 19.2 (CH_2), 14.2 (CH_3); LRMS m/z (%)+CI 198 (M^+, 30 %), 184 (100), 168 (20), 150 (20), 126 (10), 96 (10); HRMS calcd for $C_{10}H_{14}O_4$ (M+H) 198.0898, found 198.0883.

Enantiomeric excess of **110q** was determined by ^{1}HNMR analysis of the Mosher's ester derivative. **General procedure for the preparation of MTPA ester**: To a solution of furanone **210q** (10 mg, 5 x 10^{-5} mol) and DMAP (12.4 mg, 0.10 mmol) in dry dichloromethane (3.0 mL) was added (*S*)-MTPACl (15.0 μL, 8.3 x 10^{-5} mol) and the mixture was stirred at 20 °C for 1 h. The mixture was quenched by the addition of water (1.0 mL) and ether (3.0 mL) and stirred for 15 min. The mixture was washed with aqueous hydrochloric acid (4.0 mL, 1.0 M), aqueous sodium hydroxide (4.0 mL, 1.0 M), and brine (4.0 mL) and then dried over $MgSO_4$. Filtration and evaporation gave the corresponding MTPA ester, which was characterised by ^{1}H NMR without further purification (75%). The vinyl peak for the major enantiomer was at 4.70 ppm and for the minor enantiomer at 4.61 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.42 (2H, m, phenyl), 7.37 (3H, m, phenyl), 5.30 (1H, t, J = 7.0 Hz, CHOH), 4.70 (1H, s, *CH*=C *major enantiomer*), 4.61 (1H, s, *CH*=C *minor enantiomer*), 4.13 (2H, q, J = 7.2 Hz, OCH_2), 3.49 (3H, s, OCH_3), 2.40 (1H, m, CH*H*), 2.22 (1H, m, *CH*H), 2.00 (2H, m, CH_2), 1.87 (2H, m, CH_2) 1.35 (3H, t, J = 7.2 Hz, CH_3).

(*R*)-2-Hydroxymethyl-2-methyl-5-propylfuran-3-one (110b). To a stirred solution of 1,2-dihydroxy-2-methyloct-4-yn-3-one (0.30 g, 1.76 mmol) in acetone (30 mL, HPLC grade) at 20 °C was added acidified mercury oxide solution (0.45 mL, 0.1 M HgO in 2.5% H_2SO_4). The mixture was stirred for 30 min then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was dissolved in ether (15 mL) and the solution was washed with water (25 mL). The aqueous layer was extracted with ether (2 x 15 mL) and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (30 mL), then brine (30 mL), dried over Na_2SO_4 and filtered. Evaporation gave a residue which was purified by flash

column chromatography on silica gel (30:70 ethyl acetate: petroleum ether) to give **110b** as an orange oil (0.28 g, 93%); IR ν_{max} (cm^{-1}) 3485 (OH), 1682 (C=O), 1650 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.35 (1H, s, *CH*=C), 3.76 (1H, d, J = 11.5, CH*H*OH), 3.62 (1H, d, J = 11.5, *CH*HOH), 2.44 (2H, t, *J* = 7.0, CH_2), 1.64 (2H, m, CH_2CH_3), 1.32 (3H, s, CH_3), 0.96 (3H, t, *J* = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 206.2 (C=O), 193.7 (O*C*=CH), 102.8 (*CH*=C), 90.8 (CH_3CO), 65.4 (CH_2OH), 32.7 (CH_2), 19.5 (CH_2), 18.1 (CH_3), 13.6 (CH_3); LRMS m/z (%)+CI 171 (M+, 55 %), 169 (15), 155 (11), 141 (100), 137 (15), 113 (15); HRMS calcd for $C_9H_{14}O_3$ (M+H) 171.1016, found 171.1013.

Enantiomeric excess of **110b** was determined by HPLC analysis using a Chiralcel OD column (10:90 isopropanol: *n*-hexane, λ=254 nM).

(*R*)-2-((S)-1-Hydroxypropyl)-2-methyl-5-propylfuran-3-one (110g). (*3R,4S*)-3,4-dihydroxy-4-methyl-dec-6-yn-5-one (0.30 g, 1.5 mmol) in acetone (30 mL, HPLC grade) at 20 °C was added acidified mercury(II) sulfate solution (0.1 M obtained by dissolving yellow mercury(II) oxide in aqueous 2.5% H_2SO_4). The mixture was stirred for 30 min then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was worked up as described for **110b** and then purified by column chromatography on silica gel (1:9 ethyl acetate: petroleum ether) to give **110g** (0.24 g, 80%) as a pale yellow oil; $[\alpha]_D$ = + 75.4 (c 0.13 in $CHCl_3$); IR ν_{max} (cm^{-1}) 3436 (OH), 1683 (C=O), 1653 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.43 (1H, s, C=*CH*), 3.66 (1H, t, *J* = 7.5, C*H*OH), 2.69 (1H, bs, CHO*H*), 2.53 (2H, t, *J* = 7.5, C=CCH_2), 1.71 (3H, m, C*H*HCH$_3$, CH_2CH_3), 1.44 (3H, s, CCH_3), 1.37 (1H, m, CH*H*CH$_3$), 1.07 (6H, t, *J* = 7.5, 2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 207.5 (C=O), 193.8 (*C*=CH), 103.4 (C=*C*H), 91.9 (O*C*C=O), 76.1 (CHOH), 33.1 (CH_2C=C), 24.0 (CH_2CH_3), 19.0 (CH_2), 19.1 (CH_3), 14.5 (CH_3), 10.8 (CH_3); LRMS m/z (%)+FAB 199 (100), 181 (5), 141 (75), 111 (7), 83 (5), 69 (10), 43 (15); HRMS calcd for $C_{11}H_{18}O_3$ (M+H) 199.1334, found 199.1333.

Enantiomeric excess of **110g** was determined by HPLC analysis using a Chiralcel OD column (10:90 isopropanol: *n*-hexane, λ=254 nM).

(*R*)-2-((*S*)-1-Hydroxypropyl)-2-methyl-5-phenylfuran-3-one (110h). 4,5-dihydroxy-4-methyl-1-phenylhept-1-yn-3-one (0.30 g, 1.14 mmol) was reacted as for **110b** to give a residue which was purified by flash column chromatography on silica gel (30:70 ethyl acetate: petroleum ether) to give **110h** (0.29 g, 97%) as white needles; m.p. 114-116 °C; $[\alpha]_D$ = + 120.4 (c 0.04, $CHCl_3$); IR ν_{max} (cm^{-1}) 3406 (OH), 1678 (C=O), 1647 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.85 (2H, m, Ph), 7.55 (3H, m, Ph), 6.02 (1H, s, *CH*=C), 3.73 (1H, t, *J* = 8.0, *CH*OH), 1.75-1.38 (2H, m, CH_2), 1.55 (3H, s, CH_3), 1.03 (3H, t, *J* = 7.5, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 210.3 (C=O), 185.0 (CH=*C*O), 132.9 (*ipso*-phenyl), 128.9 (phenyl), 128.8 (phenyl), 127.2 (phenyl), 100.6 (*CH*=C), 91.7 (CH_3*C*O), 76.2 (CHOH), 30.1 (CH_2), 23.9 (CH_3), 1.8 (CH_3); LRMS m/z (%)+CI 233 (M+H, 40 %), 231 (15), 229 (14), 227 (20), 225 (10), 215 (7), 203 (20), 176 (20), 175 (100), 174 (10); HRMS calcd for $C_{14}H_{16}O_3$ 233.1172 (M+H), found 233.1173; found C, 71.77; H, 6.92 ($C_{14}H_{16}O_3$ requires C, 73.15; H, 7.37).

Enantiomeric excess of **110h** was determined by HPLC analysis using a Chiralcel OJ column (50:50 ethanol: *n*-hexane, λ=210 nM), the major enantiomer eluting after 5.32 min and the minor enantiomer after 6.84 min.

***N*-Methoxy-*N*-methyl-2-dimethylacrylamide (124).** Isobutyl chloroformate (7.94 g, 58.1 mmol) was added to a solution of methacrylic acid (5.0 g, 58.1 mmol) and 4-methylmorpholine (11.8 g, 0.12 mol) in anhydrous dichloromethane (200 mL) at 0 °C. After stirring for 20 min, *N,O*-dimethylhydroxylamine hydrochloride (5.70 g, 58.1 mmol) was added and the resulting solution was stirred at 0 °C for 20 min, then at 20 °C for 2 h. The mixture was partitioned between water (100 mL) and dichloromethane (2 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give **124** (4.80 g, 64%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.29 and 5.22 (2H, m, CH_2=C), 3.64 (3H, s, CH_3O), 3.22 (3H, s, CH_3N), 1.97 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.6 (C=O), 140.2 (*C*=CH_2), 117.4 (C=*CH*$_2$), 61.2 (OCH_3), 33.3 (NCH_3), 19.9 (CH_3). The spectroscopic data are identical to those reported in the literature.[45]

(*R*)-2,3-Dihydroxy-*N*-Methoxy-2,*N*-dimethylpropionamide (125).[46] To a stirred solution of modified ADmix-α (16.0 g, containing an additional 42.0 mg of

potassium osmate plus an additional 0.45 g of the chiral ligand $(DHQD)_2PHAL$) in 1:1 *tert*-butyl alcohol-water (60 mL) at 0 °C was added the *N*-methoxy-2,*N*-dimethylacrylamide (1.50 g, 11.6 mmol). The mixture was stirred until the reaction was complete, as determined by TLC (~ 24 h). Ethyl acetate (50 mL) was added followed by sodium metabisulfite (22.0 g) and the solution was allowed to warm to 20 °C with stirring. The separated aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (100% ethyl acetate) gave **125** (1.50 g, 55%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.57 (1H, bs, OH), 3.91 (1H, d, J = 11.0, C=C*H*H), 3.61 (1H, d, J = 11.0, C=CH*H*), 3.74 (3H, s, OCH_3), 3.28 (3H, s, NCH_3), 2.66 (1H, bs, OH), 1.36 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.5 (C=O), 76.0 (COH), 67.8 (CH_2OH), 61.0 (OCH_3), 33.6 (NCH_3), 21.5 (CH_3).

(*R*)-3-(*tert*-Butyldimethylsilanyloxy)-2-hydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (126). Imidazole (3.34 g, 49.1 mmol) and *tert*-butyldimethylsilyl chloride (4.40 g, 29.4 mmol) were added to a stirred solution of 2,3-dihydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (2.0 g, 12.3 mmol) in dry dichloromethane (100 mL) at 0 °C. The cloudy mixture was stirred at 20 °C for 14 h. Water (50 mL) was added and the resulting mixture was extracted with dichloromethane (3 x 50 mL); the combined organic layers were washed with brine (50 mL) and then dried ($MgSO_4$), filtered and evaporated. Purification by flash column chromatography (20:80 ethyl acetate: hexane) gave **126** (1.60 g, 60%) as a colourless oil; $[\alpha]_D$ = + 10.9 (c 0.05, $CHCl_3$); IR ν_{max} (cm^{-1}) 3520 (OH), 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.03 (1H, d, J = 10.0, C*H*HOTBS), 3.73 (3H, s, OCH_3), 3.60 (1H, d, J = 10.0, CH*H*OTBS), 3.27 (3H, s, NCH_3), 1.34 (3H, s, CH_3), 0.85 (9H, s, $SiC(CH_3)_3$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 174.7 (C=O), 76.4 (COH), 69.0 (OCH_2), 60.8 (OCH_3), 33.8 (NCH_3), 25.8 ($SiC(CH_3)_3$), 21.2 (CH_3), 18.2 ($SiC(CH_3)_3$), -3.6 ($Si(CH_3)_2$); LRMS m/z (%)+CI 278 (M^+, 10 %), 264 (20), 220 (10), 195 (35), 173 (30), 137 (65), 120 (70), 89 (50); HRMS calcd for $C_{12}H_{27}NO_4Si$ (M+H) 278.1787, found 278.1779.

(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-2-hydroxy-2-methyloct-4-yn-3-one (127). A solution of pent-1-yne (1.50 g, 22.0 mmol) in dry tetrahydrofuran (25 mL) was treated dropwise at 20 °C with a solution of *n*-butyllithium (5.0 mL, 12.5 mmol, 2.5 M in hexanes). The mixture was stirred at 20 °C for 30 min and then added slowly to a stirred solution of 3-(*tert*-butyldimethylsilanyloxy)-2-hydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (1.60 g, 5.86 mmol) in tetrahydrofuran (25 mL). The mixture was stirred at 20 °C for 20 min and then poured into saturated aqueous ammonium carbonate (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel (5:95 ethyl acetate: petroleum ether) to give **127** (1.30 g, 78%) as a pale yellow oil; $[\alpha]_D = +$ 24.4 (c 0.04 in $CHCl_3$); IR ν_{max} (cm^{-1}) 3502 (OH), 2208 (alkyne group), 1692 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.03 (1H, d, J = 10.0, C*H*HOTBS), 3.56 (1H, d, J = 10.0, CH*H*OTBS), 2.39 (2H, t, J = 7.0, C≡CCH_2), 1.64 (2H, sextet, J = 7.0, CH_2), 1.33 (3H, s, CH_3), 1.02 (3H, t, J = 7.0, CH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 0.04 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 191.0 (C=O), 99.2 (*C*≡CCO), 80.4 (COH), 78.4 (C≡*C*CO), 69.0 (OCH_2), 25.7 (SiC(CH_3)$_3$), 21.1 (CH_2), 20.6 (CH_2), 18.2 (CH_3), 13.5 (CH_2CH_3), -3.6 Si(CH_3)$_2$; LRMS m/z (%)+CI 285 (M^+, 85 %), 267 (90), 227 (35), 173 (8), 131 (5); HRMS calcd for $C_{15}H_{28}O_3Si$ (M+H) 285.1886, found 285.1878.

(*R*)-2-(*tert*-Butyldimethylsilanyoxymethyl)-2-methyl-5-propylfuran-3-one (128). To a stirred solution of 1-(*tert*-butyldimethylsilanyloxy)-2-hydroxy-2-methyloct-4-yn-3-one (0.50 g, 1.76 mmol) in acetone (30 mL, HPLC grade) at 20 °C was added acidified mercury(II) sulfate solution (0.45 mL, 0.1 M obtained by dissolving yellow mercury(II) oxide in aqueous 2.5% H_2SO_4). The mixture was stirred for 30 min then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was dissolved in diethyl ether (20 mL) and the solution we washed with water (20 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL), and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (30 mL), then brine (30 mL), and dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography on silica gel (10:90 ethyl acetate:

petroleum ether) to give **128** (0.46 g, 92%) as a yellow oil; $[\alpha]_D$ = – 112.9 (c 0.05, $CHCl_3$); IR (KBr, cm^{-1}) ν_{max} 1687 (C=O), 1645 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.38 (1H, s, *CH*=C), 3.76 (1H, d, *J* = 11.0, C*H*HOTBS), 3.70 (1H, d, *J* = 11.0, CH*H*OTBS), 2.47 (2H, t, *J* = 7.5, CH_2), 1.68 (2H, sextet, *J* = 7.5, CH_2), 1.28 (3H, s, CH_3), 0.99 (3H, t, *J* = 7.5, CH_3), 0.83 (9H, s, SiC(CH_3)$_3$), 0.01 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 205.5 (C=O), 193.1 (*C*=CHCO), 102.8 (C=*CH*CO), 91.2 (O*CH*), 66.1 (*CH*$_2$OTBS), 32.7 (CH_2), 25.7 (SiC(CH_3)$_3$), 19.6 (CH_2), 18.2 (Si*C*(CH_3)$_3$), 17.8 (CH_2), 13.7 (CH_3), -3.6 (Si(CH_3)$_2$); LRMS m/z (%)+CI 285 (M^+, 100 %), 269 (40), 227 (70), 199 (5); HRMS calcd for $C_{15}H_{28}O_3Si$ (M+H) 285.1886, found 285.1891.

(*R*)-2-Hydroxymethyl-2-methyl-5-propylfuran-3-one (110b). To a stirred solution of 2-(*tert*-butyldimethylsilanyoxymethyl)-2-methyl-5-propylfuran-3-one (0.40 g, 1.41 mmol) in methanol (17 mL) at 20 °C was added hydrochloric acid (2.8 mL, 1.0 M). After 24 h, the methanol was evaporated and the aqueous residue was extracted with ether (3 x 5 mL). The organic layers were then washed with 5% aqueous sodium carbonate (2 x 5 mL) followed by brine (5 mL), and then dried over $MgSO_4$, filtered and evaporated. Flash column chromatography (30:70 ethyl acetate: petroleum ether) gave **110b** (0.20 g, 83%) as an orange oil; $[\alpha]_D$ = + 67.1 (c 0.07, $CHCl_3$). The spectroscopic data was identical to that of **110b** stated earlier.

Enantiomeric excess of **110b** was determined by ^{1}HNMR analysis of the Moshers ester derivative, prepared by the general procedure described for **110q**. The vinyl peak for the major enantiomer was at 5.36 ppm and for the minor enantiomer at 5.43 ppm; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.46 (2H, m, phenyl), 7.40 (3H, m, phenyl), 5.43 (1H, s, CH=C *minor enantiomer*), 5.36 (1H, s, CH=C *major enantiomer*), 4.47 (2H, m, CH_2O), 3.50 (3H, s, OCH_3), 2.33 (2H, t, *J* = 7.6 Hz, *CH*$_2$C=CH), 1.53 (2H, m, CH_2), 1.38 (3H, s, CH_3), 0.92 (3H, t, *J* = 7.6 Hz, CH_3).

(*S*)-(-)-2-Acetoxysuccinic anhydride (132).[63] A mixture of (*S*)-malic acid (3.2 g, 23.9 mmol) and acetyl chloride (26.5 g, 0.34 mol) was heated to 40 °C with stirring for 2 h. The excess acetyl chloride and acetic acid/anhydride were removed *in vacuo*. The white residue (3.6 g, 95%) of **132** was used in the next step without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.72 (1H, dd, *J* = 9.0 and 6.0

Hz, OCH), 3.37 (1H, dd, J = 19.0 and 9.0 Hz, C*H*HCO), 3.01 (1H, dd, J = 19.0 and 6.0 Hz, CH*H*CO), 2.19 (3H, s, CH_3C=O); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.6 (CH_3C=O), 167.1 (C=O), 166.1 (C=O), 67.5 (OCH), 35.1 (CH_2O), 20.2 (CH_3).

(*S*)-3-Acetoxy-4-oxodec-5-ynoic acid (133). To a stirred solution of (*S*)-(-)-2-acetoxysuccinic anhydride (2.0 g, 12.7 mmol) in tetrahydrofuran (10 mL) at – 78 °C was added dropwise during 25 min a freshly prepared solution 1-lithio hexyne (prepared by treating a solution of *n*-hexyne (0.93, 11.4 mmol) in tetrahydrofuran (8 mL) with a *n*-butyllithium (4.6 mL, 11.4 mmol, 2.5 M in hexanes) at – 78 °C, followed by stirring for 30 min). After addition, the mixture was stirred for 10 min, then quenched by addition to saturated aqueous ammonium chloride (20 mL). The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to give crude **133** (2.3 g, 76%) as a red oil; $[\alpha]_D$ = – 24.5 (c 0.14, $CHCl_3$); IR ν_{max} (cm^{-1}) 3510 (CO_2H), 2214 (alkyne group), 1680 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.94 (1H, bs, CO_2H), 5.48 (1H, t, J = 4.0 Hz, O*CH*), 3.05 (1H, dd, J = 17.0 and 4.0 Hz, CH*H*CO_2H), 2.86 (1H, dd, J = 17.0 and 8.0 Hz, C*H*HCO_2H),), 2.40 (2H, t, J = 7.0 Hz, CH_2C≡C), 2.16 (3H, s, CH_3C=O), 1.57 (2H, m, CH_2), 1.44 (2H, m, CH_2CH_3), 0.92 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 182.1 (C=O), 174.9 (COOH), 169.7 (CH_3C=O), 99.7 (*C*≡CCO), 78.0 (C≡*C*CO), 74.4 (OCH), 35.1 (CH_2), 29.5 (CH_2), 21.9 (CH_2), 20.5 (CH_3), 18.8 (CH_2), 13.4 (CH_3); LRMS m/z (%)+CI 241 (M+H, 52 %), 223 (40), 199 (15), 181 (100), 163 (70), 137 (20), 109 (55), 81 (9), 61 (12); HRMS calcd for $C_{12}H_{16}O_5$ 241.1076 (M+H), found 241.1078.

(*S*)-2-Trifluoroacetoxyl succinic anhydride (134).[64] (*S*)-Malic acid (1.90 g, 14.9 mmol) was placed in a 20 mL round-bottomed flask and cooled to 0 °C. Trifluoroacetic anhydride (4 mL, 32.8 mmol) was added and the suspension was stirred, within 15 min the solution became homogenous. After 2 h at 0 °C, the trifluoroacetic acid formed and excess trifluoroacetic anhydride were removed by vacuum distillation to give **134** (2.25 g, 75%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.90 (1H, dd, J = 9.5 and 7.5 Hz, C*H*OH), 3.54 (1H, dd, J = 19.0 and 9.5 Hz, C*H*HC=O), 3.22 (1H, dd, J = 19.0 and 7.5 Hz, CH*H*C=O); ^{13}C NMR (75 MHz,

$CDCl_3$) δ_C 170.5 (C=O), 168.3 (C=O), 167.6 (C=O), 123.6 (CF_3), 69.5 (OCH), 30.7 (CH_2CO).

(*S*)-3-Hydroxy-4-oxodec-5-ynoic acid (130). To a stirred solution of (*S*)-(-)-2-trifluoroacetoxysuccinic anhydride (2.0 g, 9.43 mmol) in tetrahydrofuran (10 mL) at – 78 °C was added dropwise during 25 min a freshly prepared solution of lithiated hex-1-yne (prepared by treating a solution of *n*-hexyne (0.70 g, 8.5 mmol) in tetrahydrofuran (8.0 mL) with *n*-butyllithium (3.43 mL, 8.58 mmol, 2.5 M in hexanes) at – 78 °C followed by stirring for 30 min). After addition, the mixture was stirred for 10 min and then quenched by addition to saturated aqueous ammonium chloride (20 mL). Then the aqueous layer was extracted with ether (3 x 20 mL) and the organic layers were dried over $MgSO_4$, filtered and evaporated to give **130** (0.93 g, 50%) as a red oil; $[\alpha]_D$ = + 75.8 (c 0.06 in $CHCl_3$); IR ν_{max} (cm^{-1}) 3485 (CO_2H), 3369 (OH), 2212 (alkyne group), 1683 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.00 (1H, bs, COOH), 4.66 (1H, dd, *J* = 7.0 and 4.0, *CH*OH), 3.03 (1H, dd, *J* = 16.6, 4.0, *CH*HCOOH), 2.81 (1H, dd, *J* = 16.6 and 7.0, CH*H*COOH), 2.42 (2H, t, *J* = 7.0, CH_2C≡C), 1.60-1.38 (4H, m, CH_2CH_2), 0.91 (3H, t, *J* = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 186.8 (C=O), 175.8 (COOH), 101.7 (*C*≡CCO), 83.0 (C≡*C*CO), 74.5 (CHOH), 38.2 (CH_2COOH), 29.6 (CH_2), 21.9 (CH_2), 18.9 (CH_2), 13.4 (CH_3); LRMS m/z (%)+CI 199 (M^+, 75 %), 181 (71), 155 (100), 137 (70), 109 (70), 99 (20), 85 (30), 69 (20); HRMS calcd for $C_{10}H_{14}O_4$ (M+H) 199.0970, found 199.0961.

((*S*)-5-Butyl-3-oxo-2,3-dihydrofuran-2-yl) acetic acid (129). To a stirred solution of 3-hydroxy-4-oxodec-5-ynoic acid (0.20 g, 1.01 mmol) in acetone (20 mL, HPLC grade) at 20 °C was added acidified mercury sulfate solution (0.45 mL, 0.1 M obtained by dissolving yellow mercury^{II} oxide in aqueous 2.5% H_2SO_4). The mixture was stirred for 30 min then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was dissolved in ether (15 mL) and the solution was washed with water (25 mL). The aqueous layer was extracted with ether (2 x 15 mL), and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (30 mL) then brine (30 mL), and dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography (30:70 ethyl acetate:

petroleum ether) to give **129** (0.16 g, 80%) as a yellow oil; $[\alpha]_D$ = + 25.0 (c 0.03 in MeOH); IR ν_{max} (cm^{-1}) 3546 (OH), 1673 (C=O), 1648 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.70 (1H, bs, COOH), 5.51 (1H, s, CH=C), 4.82 (1H, dd, *J* = 9.0 and 3.4, OCH), 3.04 (1H, dd, *J* = 17.0 and 3.4, C*H*HCOOH), 2.63 (1H, dd, *J* = 17.0 and 9.0, CH*H*COOH), 2.51 (2H, t, *J* = 7.5, $CH_2C{\equiv}C$), 1.61 (2H, m, CH_2), 1.40 (2H, m, CH_2), 0.93 (3H, t, *J* = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 203.4 (C=O), 195.1 (*C*=CH), 174.4 (COOH), 103.2 (C=*C*H), 81.4 (OCH), 35.7 (CH_2CO_2H), 30.5 (CH_2), 28.0 (CH_2), 22.2 (CH_2), 13.6 (CH_3); LRMS m/z (%)+CI 199 (M^+, 100 %), 181 (40), 153 (40), 127 (20), 99 (10), 85 (50), 69 (10), 58 (60); HRMS calcd for $C_{10}H_{14}O_4$ (M+H) 199.0970, found 199.0959.

Ethyl (*E*)-3-(methoxymethylcarbamoyl)-acrylate (136). Isobutyl chloroformate (0.95 g, 6.94 mmol) was added to a solution of but-2-enedioic acid monoethyl ester (1.0 g, 6.94 mmol) and 4-methylmorpholine (1.40 g, 13.9 mmol) in dichloromethane (50 mL) at 0 °C. After stirring for 20 min, *N, O*-dimethylhydroxylamine hydrochloride (0.70 g, 6.94 mmol) was added and the resulting solution was stirred at 0 °C for 20 min, then at 20 °C for 2 h. The mixture was partitioned between water (50 mL) and dichloromethane (2 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give **136** (1.10 g, 85%) as a light red oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.70 (1H, d, *J* = 15.5, *CH*=CHCO), 6.90 (1H, d, *J* = 15.5, CH=*CH*CO), 4.26 (2H, q, *J* = 7.0, OCH_2), 3.73 (3H, s, OCH_3), 3.27 (3H, s, NCH_3), 1.31 (3H, t, *J* = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 165.6 (C=O), 164.7 (C=O), 132.5 (CH=*CH*CO), 131.6 (*CH*=CHCO), 62.2 (OCH_3), 61.2 (OCH_2), 32.4 (NCH_3), 14.1 (CH_3). The spectroscopic data are identical to those reported in the literature.[65]

Ethyl (*E*)-4-oxodec-2-en-5-ynoate (137). A solution of hex-1-yne (1.45 g, 17.6 mmol) in dry tetrahydrofuran (25 mL) was treated dropwise at -78 °C with a solution of *n*-butyllithium in hexanes (4.8 mL, 12.0 mmol, 2.5 M). The mixture was stirred at -78 °C for 30 min. This mixture was then added to a solution of ethyl (*E*)-3-(methoxymethylcarbamoyl)-acrylate (1.50 g, 8.02 mmol) in dry tetrahydrofuran (100 mL). The mixture was stirred at -78 °C for 1 h, and then poured into saturated aqueous ammonium carbonate (30 mL). The layers were separated and the aqueous

layer was extracted with ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (5:95 ethyl acetate: petroleum ether) to give **137** (0.60 g, 39%) as an orange oil; IR ν_{max} (cm^{-1}) 2227 (alkyne group), 1691 (C=O), 1643 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.92 (2H, m, CH=CH), 4.25 (2H, m, CH_2O), 2.44 (2H, t, J = 7.0, CH_2), 1.61 (2H, m, CH_2), 1.44 (2H, m, CH_2), 1.36 (3H, t, J = 7.0, CH_3), 0.94 (3H, t, J = 7.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 177.3 (C=O), 156.1 (EtO*C*=O), 141.0 (CH=*CH*CO), 135.2 (*CH*=CHCO), 97.2 (*C*≡CCO), 79.1 (C≡*C*CO), 61.6 (OCH_2), 29.7 (CH_2), 22.0 (CH_2), 19.0 (CH_3), 18.8 (CH_2), 13.5 (CH_3); LRMS m/z (%)+CI 209 (M+H, 15 %), 196 (40), 166 (22), 146 (10), 135 (20), 109 (100), 91 (10), 79 (25), 65 (10), 53 (15); HRMS calcd for $C_{12}H_{16}O_3$ 209.1178 (M+H), found 209.1174.

Ethyl-4-hydroxybut-2-enoate (138).[66] But-2-enedioic acid monoethyl ester (3.0 g, 20.8 mmol) was dissolved in anhydrous THF (90 mL) at 0 °C under an atmosphere of nitrogen, the mixture was treated with $(CH_3)_2S.BH_3$ (17.7 mL, 35.4 mmol, 2.0 M in THF). After 2 h, water (12 mL) was carefully added, followed by K_2CO_3 (2.4 g). The reaction mixture was extracted with ether (3 x 60 mL). The residue obtained after evaporation of the dried organic layers provided **138** (2.1 g, 69%) as a pale yellow oil, which was used in the next step without further purifications.

Ethyl-4-oxobut-2-enoate (139).[67] Ethyl-4-hydroxybut-2-enoate (0.40 g, 3.1 mmol) was reacted as for **108a** to give a residue that was purified by flash column chromatography (10:90, ethyl acetate: hexanes) to give **139** (0.20 g, 51%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.74 (1H, d, J = 7.0 Hz, CHO), 6.92 (1H, dd, J = 7.0 and 16.0 Hz, CH=*CH*C=O), 6.73 (1H, d, J = 16.0 Hz, *CH*=CHCO), 4.23 (2H, q, J = 7.0 Hz, OCH_2), 1.28 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 192.5 (C=O), 164.8 (EtO*C*=O), 140.3 (CH=*CH*CO), 139.4 (*CH*=CHCO), 61.7 (OCH_2), 14.0 (CH_3).

Ethyl-4-oxobut-2-enoate (139).[51,68] A saturated solution of solvent red 19 in (2.15 mg, 4.3 mL, 0.05%,) ethanol was added to a solution of ethyl sorbate (6.0 g, 42.9 mmol) in ethanol (182 mL) in a 250 mL round-bottomed flask. The resultant

mixture was submitted to ozonization for 2 h, then reduction with dimethyl sulfide (6.43 mL) over 24 h at 20 °C. The solvent was evaporated to give **139** (5.3 g, 96%) as a pale yellow oil. The spectroscopic data was identical to that of **139** obtained from the previous method.

Ethyl-4-hydroxydec-2-en-5-ynoate (141). A solution of hex-1-yne (0.86 g, 10.5 mmol) in dry tetrahydrofuran (25 mL) was treated dropwise at - 78 °C with a solution of *n*-butyllithium in hexanes (3.70 mL, 14.0 mmol, 2.5 M). The mixture was stirred at - 78 °C for 30 min, the mixture was added dropwise to a solution of ethyl-4-oxobut-2-enoate (1.0 g, 11.7 mmol) in tetrahydrofuran (20 mL). The mixture was stirred at - 78 °C for 1 h and then poured into saturated aqueous ammonium chloride (30 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (30:70 ethyl acetate: petroleum ether) to give **141** (5.0 g, 68%) as an orange oil; IR ν_{max} (cm^{-1}) 3395 (OH), 2212 (alkyne group), 1621 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.89 (1H, dd, J = 4.0 and 11.0 Hz, *CH*=CHCOH), 6.12 (1H, dd, J = 2.0 and 15.0 Hz CH=*CH*COH), 5.00 (1H, s, CHOH), 4.20 (2H, q, J = 7.0 Hz, OCH_2), 3.73 (2H, m, CH_2), 2.23 (2H, m, CH_2), 1.84 (2H, m, CH_2), 1.29 (3H, t, J = 7.0 Hz, CH_3), 0.90 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.2 (C=O), 145.7 (CH=*CH*COH), 121.5 (*CH*=CHCOH), 88.3, (*C*≡CCOH), 77.5 (C≡*C*COH), 68.0 (CHOH), 61.6 (*C*H_2), 25.6 (CH_2), 22.0 (CH_2), 18.4 (CH_2), 14.2 (CH_3), 13.6 (CH_3); LRMS m/z (%)+CI 209 (100), 181 (40), 135 (30), 109 (75), 71 (38); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1261.|

Ethyl (*E*)-4-oxodec-2-en-5-ynoate (137). Ethyl-4-hydroxydec-2-en-5-ynoate (1.0 g, 4.8 mmol) was reacted as for **108a** to give a residue which was purified by column chromatography (5:95 ethyl acetate: petroleum ether) to give **137** (0.65 g, 65%) as an orange oil. The spectroscopic data were identical to that of **137** given above.

Ethyl (*2S,3S*)-2,3-dihydroxy-4-oxodec-5-ynoate (142). To a stirred solution of modified ADmix-β (7.0 g, containing an additional 14.0 mg of potassium osmate) in 1:1 *tert*-butyl alcohol-water (38 mL) was added sodium hydrogen carbonate (0.97 g,

11.5 mmol) and methanesulfonamide (0.37 g, 3.85 mmol) at 0 °C. A solution of ethyl (*E*)-4-oxodec-2-en-5-ynoate (0.80 g, 3.85 mmol) in toluene (1 mL) was added and the mixture was stirred until the reaction was complete as determined by TLC (~ 24 h). Ethyl acetate (20 mL) was added followed by sodium metabisulfite (5.8 g) and the stirred solution was allowed to warm to 20 °C. The separated aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (35 mL, 1 M), dried (Na_2SO_4), filtered and evaporated. Flash column chromatography of the residue (30:70 ethyl acetate: petroleum ether) gave **142** (0.64 g, 60%) as an orange oil; $[\alpha]_D$ = + 56.7 (c 0.02, $CHCl_3$); IR ν_{max} (cm^{-1}) 3390 (OH), 2210 (alkyne group), 1692 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.80 (1H, s, *CH*OH), 4.59 (1H, s, *CH*OH), 4.35 (2H, q, *J* = 7.0 Hz, CH_2O), 2.46 (2H, t, *J* = 7.0 Hz, CH_2C≡C), 1.59 (2H, m, CH_2), 1.46 (2H, m, CH_2), 1.35 (3H, t, *J* = 7.0 Hz, CH_3), 0.93 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 184.7 (C=O), 171.5 (EtO*C*=O), 101.9 (*C*≡CCO), 85.2 (C≡*C*CO), 79.5 (CHOH), 71.4 (CHOH), 62.6 (OCH_2), 29.5 (CH_2), 22.0 (CH_2), 19.0 (CH_2), 14.2 (CH_3), 13.5 (CH_3); LRMS m/z (%)+CI 243 (M+H, 8 %), 215 (50), 197 (20), 179 (15), 169 (20), 161 (5); HRMS calcd for $C_{12}H_{18}O_5$ 243.1232 (M+H), found 243.1244.

3-((*S*)-5-Butyl-3-oxo-2,3-dihydro-furan-2-yl)-3*S*-hydroxy-propionic acid ethyl ester (143). To a stirred solution of ethyl 2,3-dihydroxy-4-oxodec-5-ynoate (0.60 g, 2.5 mmol) in acetone (60 mL, HPLC grade) at 20 °C was added acidified mercury oxide solution (0.45 mL, 0.1 M HgO in 2.5 % H_2SO_4). The mixture was stirred for 30 min then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was dissolved in ether (15 mL) and the solution was washed with water (25 mL). The aqueous layer was extracted with ether (2 x 15 mL), and the combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (30 mL) then brine (30 mL), and dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography on silica gel (30:70 ethyl acetate: petroleum ether) to give **143** (0.37 g, 62%) as a yellow powder; $[\alpha]_D$ = − 133.3 (c 0.03, $CHCl_3$); IR ν_{max} (cm^{-1}) 3387 (OH), 1689 (C=O), 1643 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.48 (1H, s, *CH*=C), 4.78 (1H, d, *J* = 5.6, *CH*OH), 4.73 (1H,

d, J = 5.6, *CH*OH), 4.31 (2H, q, J = 7.0 Hz, OCH_2), 2.51 (2H, t, J = 7.0 Hz, CH_2), 1.60 (4H, m, CH_2), 1.36 (3H, t, J = 7.0 Hz, CH_3), 0.93 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 201.1 (C=O), 195.7 (C=*C*O), 171.7 (*C*O_2Et), 104..4 (*CH*=C), 85.8 (OCH), 69.5 (OCH), 62.7 (OCH_2), 30.4 (CH_2), 28.1 (CH_2), 22.2 (CH_2), 14.1 (CH_3), 13.7 (CH_3); LRMS m/z (%)+CI 242 (M+H, 5 %), 200 (7), 169 (100), 149 (60), 113 (10), 97 (30), 69 (15); HRMS calcd for $C_{12}H_{18}O_5$ 242.1154 (M+H), found 242.1157.

Attempted synthesis of 3-((*S*)-5-Butyl-3-oxo-2,3-dihydro-furan-2-yl)-propionic acid ethyl ester. (a) Thiocarbonyldiimidazole (0.10 g, 1.25 mmol) was added quickly to a stirred solution of furanone **152** (0.10 g, 0.41 mmol) in tetrahydrofuran (4 mL). The reaction mixture was stirred at 65 °C for 12 h, in the dark, and then the solution was evaporated. The resulting residue was dissolved in 5:1 ethyl acetate: dichloromethane (10 mL), washed successively with aqueous hydrochloric acid (2.5 mL), saturated aqueous sodium hydrogen carbonate (4 mL) and brine (4 mL), and dried over $MgSO_4$, filtered then evaporation gave the thiol (80 mg, 57 %) as a pale yellow oil.

(b) To a stirred solution of tributyltin hydride (0.25 g, 0.85 mmol) and azobisisobutyronitrile, AIBN, (7.0 mg, 4.26 x 10^{-5} mol) in toluene (5 mL) at 75 °C was added dropwise a solution of thiol (0.10 g, 0.28 mmol) in toluene (1 mL). The solution was then stirred at 75 °C for 90 min and then evaporated to give an oil, which was shown to be a mixture of components by TLC and so it was not treated further.

(*R*)-2-((*S*)-1-Hydroxy-propyl)-2-methyl-5-phenylfuran-3-one (110h). To a stirred solution of 4,5-dihydroxy-4-methyl-1-phenylhept-1-yn-3-one (75 mg, 0.32 mmol) in tetrahydrofuran (2 mL) was added $PdCl_2$ powder (1.7 mg, 6.46 x 10^{-3} mmol) at 20 °C and stirring was continued for 24 h. The reaction was quenched by the addition of pH 7 phosphate buffer (2 mL), and extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were washed with brine (3 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (30:70

ethyl acetate: petroleum ether) to give **110h** (62 mg, 0.27 mmol) as an orange oil. Spectroscopic data were identical with those described above.

Enantiomeric excess of **110h** was determined by HPLC analysis using a Chiralcel OJ column (50:50 ethanol: *n*-hexane, λ=210 nM), the major enantiomer eluting after 5.32 min and the minor enantiomer after 6.84 min.

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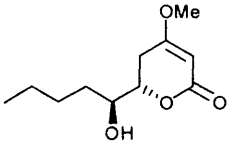
Chapter 3

Towards the Synthesis of (-)-Pestalotin using Sharpless Asymmetric Dihydroxylation

3.1. Introduction

(-)-Pestalotin **85** is a gibberellin synergist which was first isolated from the culture filtrate of the phytopathogenic fungus *Pestaltia cryptomeriaecola* by Kimuro and co-workers[1,2] it has also been obtained from an unidentified *Penicillium* species by Ellestad and co-workers.[3] Pestalotin has a 5,6-dihydro-4-methoxy-2*H*-pyran-2-one skeleton with one hydroxy group on the side-chain. The absolute configuration of the (-)-enantiomer was identified as *6S, 1S* (Figure 3.1).



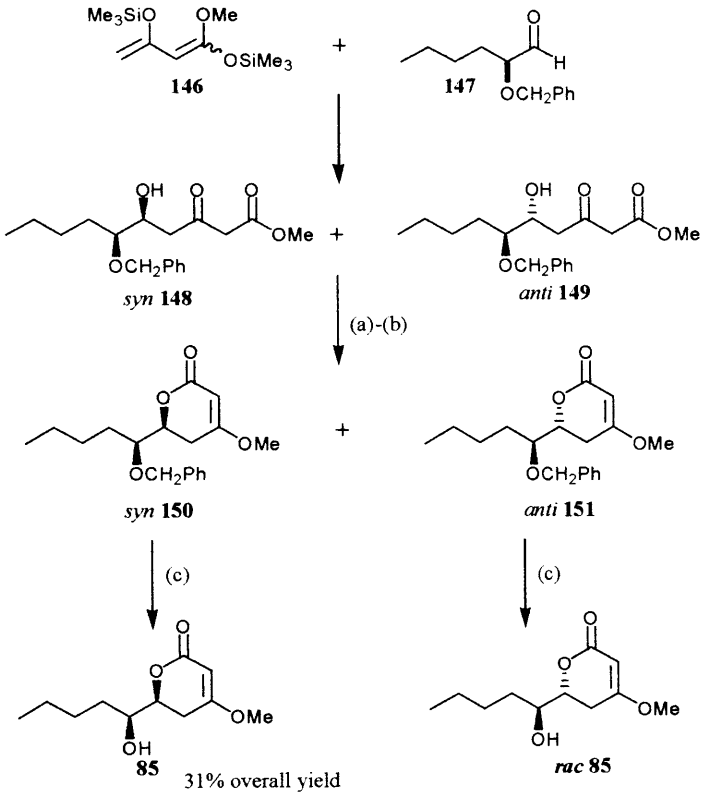
85

Figure 3.1: The structure of (-)-pestalotin.

The presence of two contiguous asymmetric centres in (-)-pestalotin **85** has made it an attractive synthetic target. To date, more than ten total syntheses of **85** have been reported, this includes the synthesis of (*rac*)-pestalotin[4,5] as well as its optically active forms,[6-16] in these syntheses the asymmetric centres were usually prepared in a stepwise manner resulting in poor diastereoselectivity.

3.2 Several Syntheses of (6S,1S)-(-)-Pestalotin Reported in the Literature

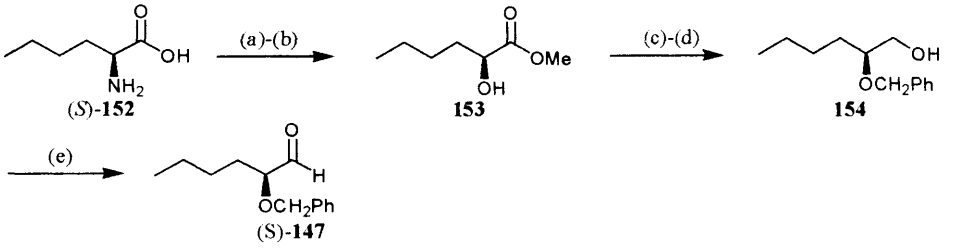
Scheme 3.1 illustrates the total synthesis of **85** carried out by Hagiwara and co-workers,[16] which applied a Lewis acid-mediated aldol addition of the *bis*-trimethylsilyl enol ether **146** with 2-benzyloxyhexanal **147** to generate the *syn* 1,2-glycol derivative **148** in high *syn*-diastereoselectivity (Table 3.1). The *syn*-diastereoselectivity was established by an intramolecular chelation of the metal cation with the carbonyl group of **147** and the neighbouring alkoxy group forming a conformationally rigid system thus allowing stereofacial control in the nucleophilic addition of the enolate **146**.



Scheme 3.1. *Reagents and conditions*: (a) $NaOH_{(aq)}$, THF, 20 °C, 30 min, then HCl; (b) Me_2SO_4, K_2CO_3, acetone, 20 °C, 45 h, 72% over two steps; (c) H_2, 5% Pd/C, EtOAc, 20 °C, 46 h, 65%.

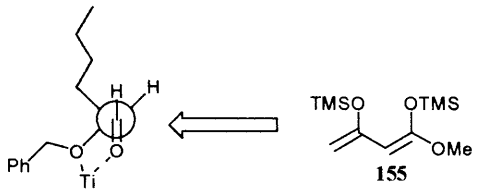
The requisite (*S*)-(-)-2-benzyloxyhexanal **147**, was prepared in five steps staring from (*S*)-(-)-2-aminohexanoic acid (*L*-norleucine, 97% optically pure) (*S*)-**152** (Scheme 3.2). (*S*)-(-)-2-Aminohexanoic acid **152** was initially treated with sodium nitrate in

dilute sulphuric acid to give (*S*)-(-)-2-hydroxyhexanoic acid. After esterification with diazomethane, methyl (*S*)-(-)-2-hydroxyhexanoate **153** was protected as the corresponding benzyl ether using benzyl bromide and silver oxide as the base, these conditions were necessary in order to avoid epimerisation at C-2.[17] The resulting (*S*)-(-)-2-benzyloxyhexanoate was reduced with lithium aluminium hydride ($LiAlH_4$) to (*S*)-(-)-2-benzyloxyhexanol **154** and this was subsequently oxidised following Swern's method to give the required (*S*)-(-)-2-benzyloxyhexanal **147**. High-pressure liquid chromatography (HPLC) analysis of the intermediate compounds indicated that no epimerisation of the 2-benzyloxy group of compound **147** occurred during the reactions described in Scheme 3.2.



Scheme 3.2. *Reagents and conditions*: (a) $NaNO_2$, H_2SO_4, H_2O, 20 °C, 23 h, 71%; (b) CH_2N_2, Et_2O, quantitative yield; (c) Ag_2O, $PhCH_2Br$, Et_2O, 35 °C, 30 min; (d) $LiAlH_4$, Et_2O, 0 °C, 30 min, 74% over two steps; (e) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, - 60 °C, 1 h, 44%.

The results of the aldol reaction of *bis*-trimethylsilyl enol ether **146** with (*S*)-(-)-2-benzyloxyhexanal **147** are summarized in Table 3.1. The highest diastereofacial selectivity (98%) was achieved when the enol ether **146** was added at - 86 °C to a solution of (*S*)-(-)-2-benzyloxyhexanal **147** and $TiCl_4$ (Table 3.1, entry 1). Also since no selectivity was observed when $TiCl_4$ was added to the mixture of **146** and **147** (Table 3.1, entry 6), it is the initial complexation of the benzyloxyaldehyde moiety of **147** with $TiCl_4$ that is responsible for the high *syn*-diastereoselectivity observed (Scheme 3.3).

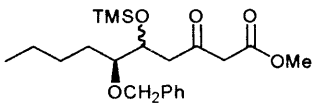


Scheme 3.3: Chelation model leading to the *syn* diastereoisomer.

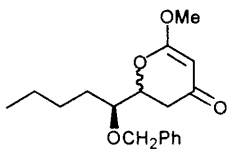
Table 3.1: Diastereoselective aldol addition to give the *syn* glycol derivative **148**.

Entry	Lewis acid	Products ratio *syn* **148** :*anti* **149**	Yield (%)
1	$TiCl_4$	99:1	66
2	$SnCl_4$	89:11	56
3	$BF_3.OEt_2$	71:29	79
4	$EtAlCl_2$	53:47	42
5	$ZnCl_2$	86:14	37
6	$TiCl_4$	54:46	80

When zinc chloride was used Table (3.1; entry 5), the trimethylsilyl ether of the aldol product, **156**, along with the pyranone **157**, a Danishefsky-type hetero Diels-Alder reaction product, were isolated in 37% and 9% yield, respectively (Scheme 3.4).



Syn- and *anti*-**156**



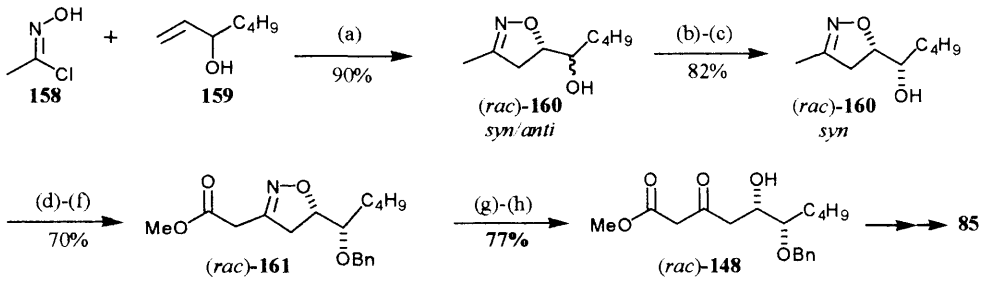
Syn- and *anti*-**157**

Scheme 3.4: Zinc chloride-mediated aldol condensation reaction.

The lactonization of an inseparable mixture of **148** and **149** followed by methylation with dimethyl sulphate gave the lactonic methyl ethers **150** and **151** (Scheme 3.1). Deprotection of the benzyl group furnished (-)-pestalotin **85** in a 31% overall yield.

Zhang and co-workers applied the isoxazoline **161** in the preparation of the β,γ-dihydroxy keto ester *rac*-**148**, a key precursor of *rac*-pestalotin (Scheme 3.5).[15]

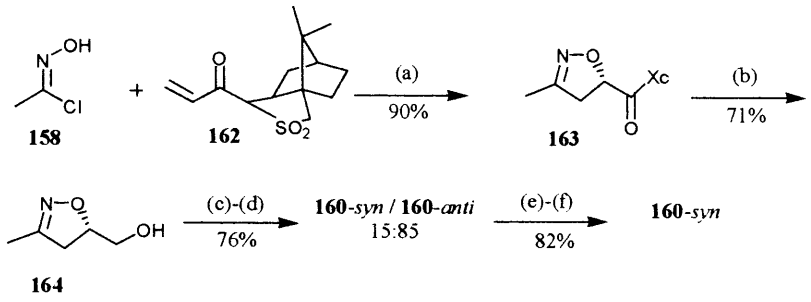
Cycloaddition of acetohydroximoyl chloride **166** with allyl alcohol **167** provides *rac*-**168** as a 1:1 mixture of *syn*- and *anti*-isomers. Swern oxidation followed by addition of excess of *L*-selectride provided *rac*-**158** as a 99:1 mixture of *syn*- and *anti*-isomers. *Rac*-**160** was benzylated, and this was followed by deprotonation of the isoxazoline **160**, carboxylation and treatment of the resulting acid with diazomethane to give *rac*-**161** in 70% yield. Reduction of *rac*-**161** with Raney Ni and hydrogen in aqueous methanol followed by brief exposure of the crude product to aqueous hydrochloric acid provided the keto ester *rac*-**148** which was converted into *rac*-pestalotin using the method described by Hagiwara and co-workers (Scheme 3.1), where the *rac*-**148** was lactonized under basic conditions, and the lactone was *O*-methylated and debenzylated to give racemic pestalotin (*rac*-**85**) in 56% overall yield.



Scheme 3.5. *Reagents and conditions*: (a) Et_3N, C_6H_6, 25 °C, 16 h; (b) $(COCl)_2$, Me_2SO, Et_3N, THF, -78 °C, 40 min; (c) *L*-Selectride, THF, -78 °C, 6 h, then NaOH and 30% H_2O_2(aq), 25 °C, 2 h; (d) NaH, BnBr, NBu_4I, THF, 25 °C, 6 h; (e) Lithium tetramethylpiperidide (LTMP), CO_2, THF, -90 °C, 4 h; (f) CH_2N_2, Et_2O, 25 °C, 1 h; (g) Raney Ni, H_2, MeOH-H_2O 15:1, 25 °C, 20 min; (h) 10% HCl, 25 °C, 15 min.

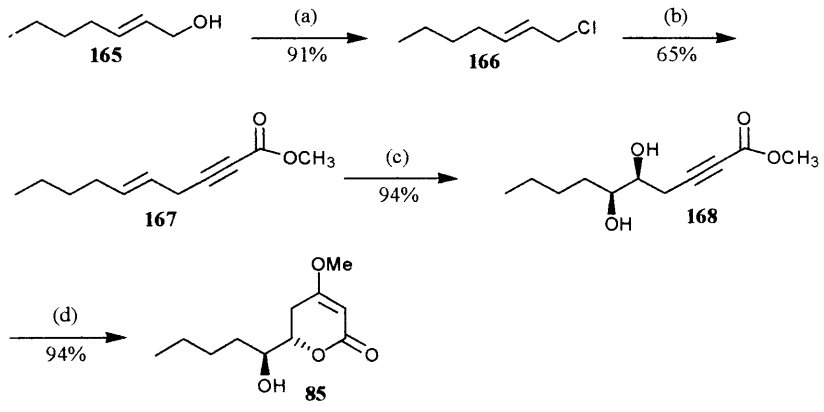
Scheme 3.6 describes the required modification to prepare enantiomerically pure **160** which was then applied in the total synthesis of (-)-pestalotin.[15] The cycloaddition of **158** and the acrylate derivative of Oppolzer's camphor sultam **162** gave the isoxazoline **163** and its diastereoisomer (not shown) in a ratio of 94:6. The auxiliary was cleaved by reduction with *L*-selectride to generate optically pure alcohol **164** (71%). Swern oxidation of **164**, followed by addition of butylmagnesium bromide provided a mixture of **160**, but enriched in the incorrect isomer for the pestalotin synthesis (*syn*/*anti*, 15:85). This mixture was subjected to Swern oxidation followed by *L*-selectride reduction to provide *syn*-**160** as a single diastereoisomer which was

isolated in 82% yield. (-)-Pestalotin **85** was then prepared using the same steps as for the racemic synthesis, outlined in Scheme 3.5.



Scheme 3.6. Xc refers to Oppolzer's auxiliary. *Reagents and conditions*: (a) Et_3N, C_6H_6, 25 °C, 12 h; (b) *L*-Selectride, THF, -78 °C, 8 h, then NaOH and 30% H_2O_2(aq), 25 °C, 2 h; (c) $(COCl)_2$, Me_2SO, Et_3N, THF, -78 °C, 40 min; (d) C_4H_9MgCl, THF, -78 °C, 4 h; (e) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, -78 °C, 40 min; (f) *L*-Selectride, THF, -78 °C, 6 h, then NaOH and 30% H_2O_2 (aq), 25 °C, 2 h.

The Sharpless asymmetric dihydroxylation (AD) reaction permits the highly stereoselective establishment of two adjacent stereogenic centres and thus has become an important reaction in natural product synthesis, including that of (-)-pestalotin (Scheme 3.7).[13]

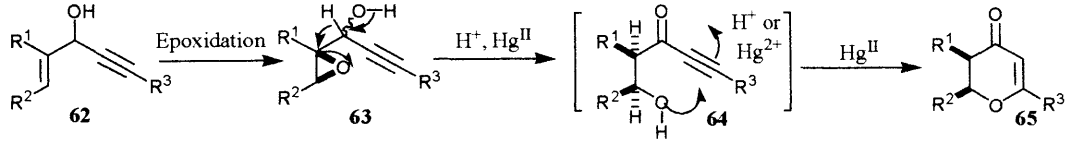


Scheme 3.7. *Reagents and conditions*: (a) CCl_4, PPh_3, 25 °C, 48 h; (b) methyl propiolate, DBU, CuI, phenothiazine, $NH_2OH.H_2O$, HMPA/THF, 60 °C, 2 h; (c) ADmix-α, $CH_3SO_2NH_2$, 0 °C, 4 h; (d) MeONa, MeOH, 0 °C, 24 h.

Wang and Shen described the synthesis of (-)-pestalotin and its enantiomer in four steps using commercially available 2-hepten-1-ol **165** as the starting material (Scheme 3.7).[13] The allylic alcohol **165** was converted to the chloride **166** using the triphenyl phosphine-carbon tetrachloride system. Reaction of **166** with methyl propiolate in the presence of CuI and DBU in a mixed solvent system (THF/ HMPA) gave the alkylated product **167** in a 65% yield. The enyne **167** was then treated with ADmix-α in the presence of methanesulfonamide to furnish the diol **168**. Treatment of **168** with NaOMe-MeOH followed by acidification afforded the lactonized Michael adduct (-)-pestalotin **85**. Its enantiomeric excess was shown to be 90% by analysis of the ^{1}H NMR data of the corresponding (*R*)-MTPA ester. The overall yield from **165** was 53%.[13] Similarly, dihydroxylation of **167** with ADmix-β instead of ADmix-α followed by Michael addition and lactonization afforded (+)-pestalotin **85** which was shown to be 95% ee by the same method mentioned above.

3.3 Results and Discussion

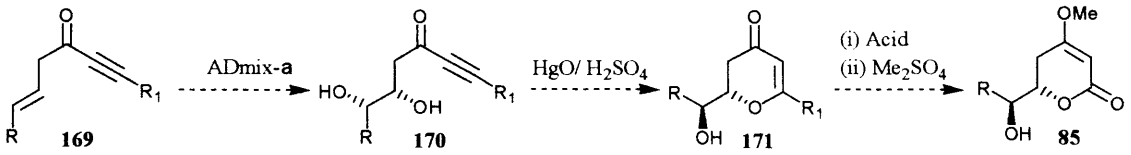
The mercury(II)-catalysed rearrangement of epoxy alkynols of type **63** into the 2,3-dihydropyran-4-one system **65** has been the focus of previous research by our group, this rearrangement may occur via a β-hydroxy alkynone intermediate such **64** (Scheme 3.8).



Scheme 3.8: Stereospecific rearrangement of epoxy alkynols to 2,3-dihydro-*4H*-pyran-4-ones.

A main limitation to the above methodology is that the synthesis of 3-unsubstituted pyranone systems (*i.e.* R^1 = H) cannot be directly attained as the initial hydride shift does not occur. A possible solution for this may be the use of substrates analogous to the proposed intermediate **64** (such as **170**) and as the ynone portion is still present, the mercury-catalysed cyclisation was predicted to occur. In this section it was proposed to use a mercury(II)-catalysed cyclisation of a β-hydroxy alkynone

intermediate **170** as the key step towards the synthesis of (-)-pestalotin **85** (Scheme 3.9).



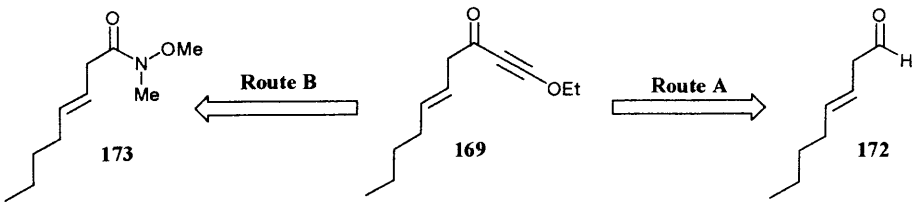
Scheme 3.9: The proposed route for the preparation of (-)-pestalotin **85**, (where R = C_4H_9, R_1 = OEt).

The cyclisation of **170** into the dihydropyranone **171** was expected to be very rapid, and may not require the presence of the $Hg^{(II)}$ catalyst due to the presence of the electron-donating (ethoxy) group attached to the alkyne unit; such reactions were previously observed with alkynyl epoxy alcohols, discussed in section 1.2.8.

The synthesis of the gibberellin synergist (-)-pestalotin **85** was to be attempted using the dihydropyran-4-one **171** by acid induced lactonisation followed by methylation of the 4-hydroxy group (Scheme 3.9).

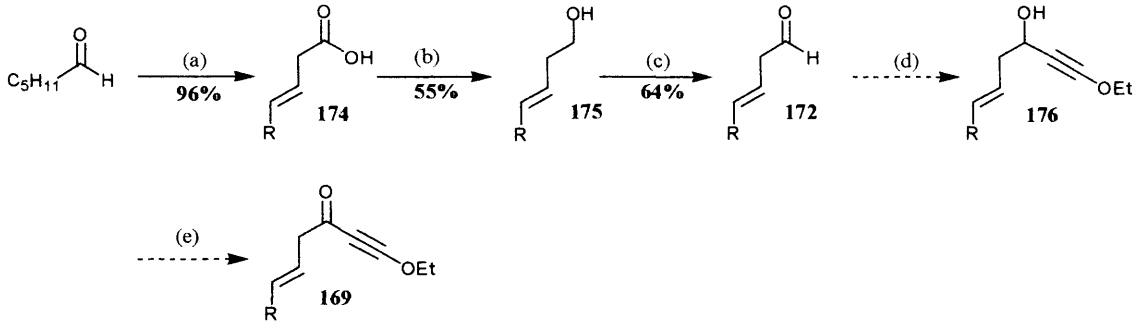
3.3.1 Attempted Preparation of the β,γ-Unsaturated Alkynone 169

The synthesis of alkynone **169** was attempted using two different methods (Scheme 3.10), route A involved the alkynylation of the corresponding β,γ-unsaturated aldehyde **172** followed by oxidation, the second synthetic route attempted was the alkynylation of the corresponding *N*-methoxy-*N*-methyl amide **173**, a Weinreb amide.



Scheme 3.10: Proposed syntheses of alkynone **169**.

The preparation of the aldehyde **172** was carried out by lithium aluminium hydride ($LiAlH_4$) reduction of the corresponding carboxylic acid **174** to give the alcohol **175**, followed by oxidation (Scheme 3.11). Different oxidation conditions were investigated to convert **175** into the aldehyde **172**; the Collins' oxidation protocol using CrO_3 and pyridine resulted in considerable isomerisation to the conjugated aldehyde. Swern oxidation ($(COCl)_2$ and Me_2SO, CH_2Cl_2, – 60 °C) also led to significant isomerisation to the conjugated aldehyde. Furthermore, DIBAL reduction of the corresponding ester (CH_2Cl_2, - 160 °C) resulted in the formation of the alcohol **175** as the main product. Due to difficulty encountered in the synthesis of **172** the synthesis of the ynone **169** using the Weinreb amide[18] was attempted.

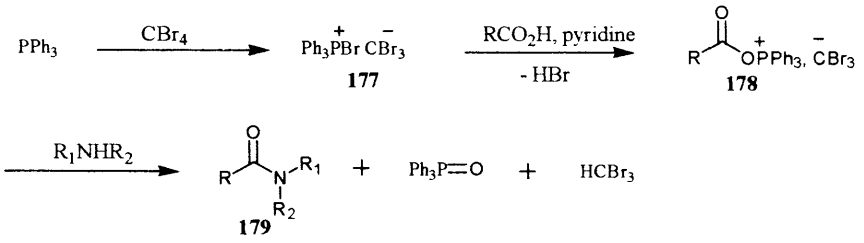


Scheme 3.11. (R = C_4H_9,). *Reagents and conditions:* (a) Malonic acid, piperidine, xylene, 140 °C, 12 h; (b) $LiAlH_4$, THF, reflux, 1 h; (c) CrO_3, pyridine, CH_2Cl_2, 20 °C, 35 min.

3.3.1.1 Preparation of Weinreb amides

Weinreb amides are versatile building blocks in organic synthesis.[19] Their preparation can be accomplished by coupling carboxylic acids and *N,O*-dimethylhydroxylamines. The majority of the methods reported use peptide coupling agents such as chloroformates,[20] BOP,[21] DCC,[22] and others[23] or phosphonic derivatives.[24-26] These reagents are expensive in some cases and the removal of their excess (and/or the removal of by-products) from the reaction mixture may be difficult. Additional purification of the reaction product is often required. The use of acid chloride,[27] ester and lactone derivatives as intermediates towards the Weinreb amide synthesis has also been popular.

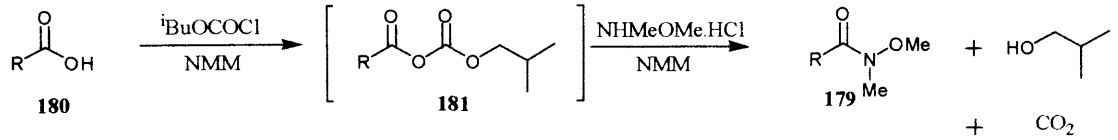
Barstow[28] and Einhorn[26] described the synthesis of Weinreb amides using the phosphonium salt **177** for activation of the acid (Scheme 3.12); the salt was generated *in situ* by the addition of triphenyphosphine to carbon tetrabromide.



Scheme 3.12: Preparation of *N*-Methoxy-*N*-methylamides using phosphonium salt **186**.

The *N,O*-dimethylhydroxylamine was conveniently used as its hydrochloride salt, an important advantage as the preparation of the free base is tedious. This procedure allowed rapid access of *N*-methoxyamides in good yields; however, the main disadvantage was the formation of the triphenylphosphine oxide by-product which complicated the purification of the final product.

A highly practical method for the preparation of *N*-methoxyamides is *via* the mixed anhydride **181**, prepared *in situ* by the addition of isobutylchloroformate to the corresponding acid in the presence of a base (*e.g.* *N*-methylmorpholine, NMM) and *N,O*-dimethylhydroxylamine. This method resulted in the rapid formation of the *N*-methoxyamide as the sole product and in excellent yields (Scheme 3.13).



Scheme 3.13: The preparation of Weinreb amides *via* the mixed anhydride methodology.

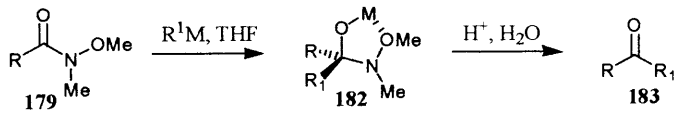
The carboxylic acid anhydrides have two carbonyl groups, either of which can theoretically participate in an aminolysis reaction to give an amide. Among the

factors that influence which of the two carbonyls undergo aminolysis are the relative electrophilicity of the carbonyl group and the steric hindrance of the activating group. Thus the carbonyl group with the lowest electron density and least steric hindrance will be the one to undergo nucleophilic attack. Complete regioselectivity was observed when isobutyl chloroformate was used to activate the carboxylic acid. Isobutyl chloroformate is also very stable to storage, in contrast to chloroformates derived from secondary alcohols. This method provides rapid reaction rates at a low temperature, high yields and the product can be recovered pure without further purification.

The alkyl chloroformate method has been widely used for peptide synthesis, as it eliminates the need to use expensive coupling reagents,[29,30] the mixed anhydrides constitute some of the most highly activated amino acid derivatives and so they are extremely efficient for peptide bond formation.

3.3.1.2 Alkynylation of Weinreb amides

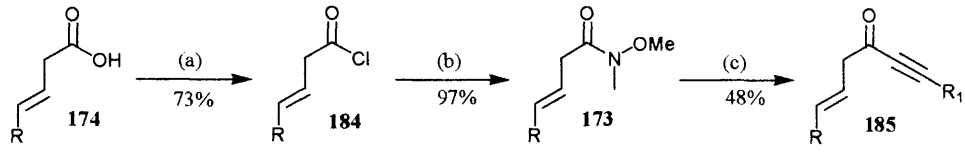
In 1981, Nahm and Weinreb reported an effective and versatile method for the conversion of *N*-methoxy-*N*-methylamides into ketones by reaction with organolithium and Grignard species in tetrahydrofuran.[18] It is believed that this conversion proceeded through a very stable metal-chelated intermediate **182** (Scheme 3.14); the inertness of **182** prevents premature release of the ketone functionality and thus avoids products from secondary addition of the nucleophile.



Scheme 3.14: Alkynylation of Weinreb amides to give ketones.

The conversion of the carboxylic acid **174** into Weinreb amide **173** was successfully carried out which provided an alternative substrate for the alkynylation reaction to give enynone **185**,[31,32] (Scheme 3.15). The *N*-methoxy-*N*-methylamide **173** was prepared from the acid chloride by employing a slight excess of the commercially

available *N,O*-dimethylhydroxylamine hydrochloride in the presence of pyridine. It was also prepared from the mixed anhydride of the carboxylic acid.[33,34] Weinreb amides have a similar stability to tertiary amides and thus require no special handling or storage.

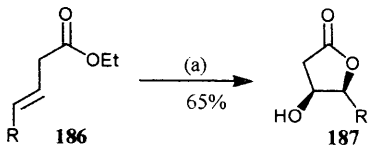


Scheme 3.15: (a) R = C_4H_9 or (b) CH_3, R_1 = C_3H_7. *Reagents and conditions*: (a) $SOCl_2$, CH_2Cl_2, 60 °C, 4 h; (b) MeNHOMe.HCl, CH_2Cl_2, 20 °C, 3 h; (c) pent-1-ynyl-lithium, THF, 20 °C, 3 h.

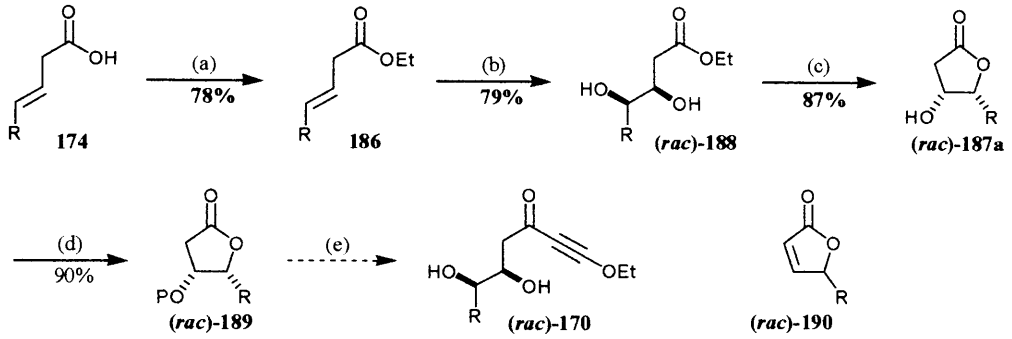
The intermediate **185** was prepared by the addition of lithium acetylide generated *in situ* by the addition of *n*-butyllithium to the terminal alkyne in anhydrous tetrahydrofuran. However, rapid isomerisation of **185** took place to form a mixture of the conjugated alkynone and **185** in a 1:2 ratio.

3.3.2 Attempted Preparation of Dihydroxy Alkynone 170

Owing to the difficulty encountered in the synthesis of the deconjugated enynone **169**, alternative synthetic routes to the diol **170** were investigated. Scheme 3.17 outlines the proposed route for the synthesis of **170**, where the alkynylation of the protected lactone **189** followed by the deprotection of the hydroxyl group was proposed to give **170**. The asymmetric dihydroxylation of ester **186** under Sharpless' conditions (Scheme 3.16)[35] is known to cause direct cyclisation to the lactone **187**. The synthesis of racemic lactone **187a** was achieved by the dihydroxylation of ester **186** using potassium osmate and *N*-methylmorpholine *N*-oxide (NMO) followed by treatment with *p*-toluenesulfonic acid.[36] This gave the lactone intermediate in a 69% yield (Scheme 3.17).[37] Unfortunately the attempted alkynylation[38-40] of the trimethylsilyl-protected lactone intermediate **189** resulted in dehydration to give the furanone by-product **190** as the sole product, this may be due to the highly acidic nature of the α-protons.



Scheme 3.16: (R = C_4H_9). *Reagents and conditions*: (a) ADmix-α, $MeSO_2NH_2$, $^tBuOH:H_2O$ (1:1), 0 °C, 40 h.

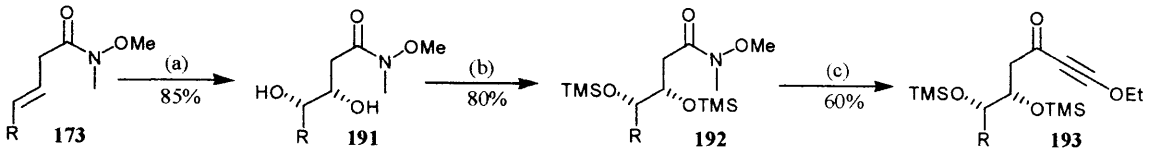


Scheme 3.17: (R = C_4H_9, P = TMS). *Reagents and conditions*: (a) H_2SO_4 (cat.), EtOH, reflux, 3 h; (b) $K_2OsO_2(OH)_4$, NMO, acetone-H_2O, 20 °C, 24 h; (c) *p*-TsOH (cat.), benzene, 50 °C, 90 min; (d) TMSCl, NEt_3, Et_2O, 20 °C, 1 h; (e) (i) ethoxyethynyl-lithium, THF, - 78 °C, (ii) HCl, MeOH, 20 °C.

The synthesis of **170** by dihydroxylation of the corresponding Weinreb amide followed by alkynylation of the protected Weinreb amide was investigated. The protected dihydroxy ynone **193** was prepared by the asymmetric dihydroxylation of the Weinreb amide **173** followed by alkynylation of the TMS protected diol **192** (Scheme 3.18).[41] The moderate yield of the alkynylation step may be attributed to partial deprotection of the labile TMS group of **192** under the basic conditions.

Asymmetric dihydroxylation of the Weinreb amide **173** was carried out using the procedure reported by Sharpless and co-workers.[42] The reagent used for this procedure was modified ADmix-α, which contained a higher percentage of the osmium catalyst (1 mol%) and the chiral ligand (5 mol%) than those commonly used. This was essential to overcome the sluggish reactivity of the Weinreb amide substrate.

The synthesis of racemic diol *rac*-**191** was achieved using potassium osmate and *N*-methylmorpholine *N*-oxide (NMO) according to the Upjohn procedure.[43]

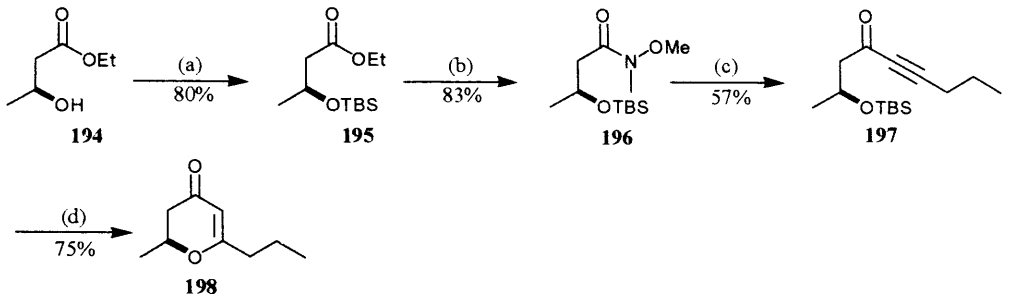


Scheme 3.18: R = C_4H_9. *Reagents and conditions*: (a) $K_2OsO_2(OH)_4$, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, ^tBuOH-H_2O, 0 °C, 12 h; (b) TMSCl, NEt_3, EtO_2, 20 °C, 12 h; (c) ethoxyethynyl-lithium, THF, - 78 °C, 3 h.

The deprotection of the TMS group was unsuccessful using either tetrabutylammonium fluoride (TBAF) in tetrahydrofuran or hydrochloric acid in methanol, a mixture of products was observed by ^1H NMR probably owing to the instability of **193** under these conditions; consequently different protecting groups were investigated, which will be discussed in the following section.

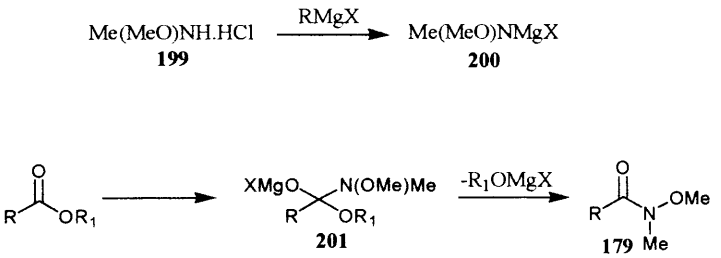
3.3.2.1 Preparation of Dihydropyranones via Weinreb amides

A model system was used to investigate the possibility of applying the mercury(II)-catalysed cyclisation on a protected β-hydroxy alkynone to give the dihydropyranone intermediate. The procedure described in Scheme 3.20 was applied for the synthesis of Weinreb amide **196** from the TBS-protected ester **195**,[44] alkynylation of the Weinreb amide followed by the mercury(II)-catalysed cyclisation furnished the dihydropyran-4-one product **198** in a 75% yield (Scheme 3.19). In order to optimise the yield of the cyclisation step it was necessary to increase the reaction time to 6 h from the usual 30 min, to allow the removal of the TBS protecting group.



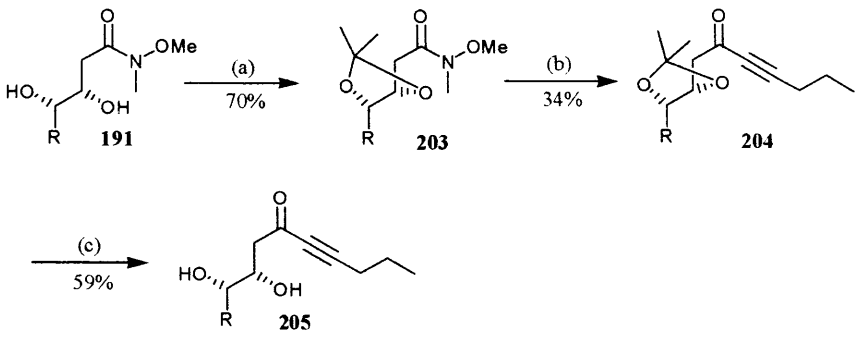
Scheme 3.19: *Reagents and conditions*: (a) TBSCl, imidazole, CH_2Cl_2, 20 °C, 3 h; (b) NHMeOMe.HCl, Et_2O, - 20 °C, ^{i}PrMgCl, 20 min; (c) pent-1-ynyl-lithium, THF, 0 °C, 2 h; (d) HgO/ H_2SO_4, acetone, 20 °C, 6 h.

The direct conversion of esters into the *N*-methoxy-*N*-methylamides is usually achieved using aluminium-based reagents.[45] Recently, the use of Grignard reagents to effect this reaction was reported by Grabawski and co-workers[46] (Scheme 3.20). ^{i}PrMgBr was the preferred base as it gave higher yields of the amide; this method was general and could also be used for enolisable as well as hindered esters.



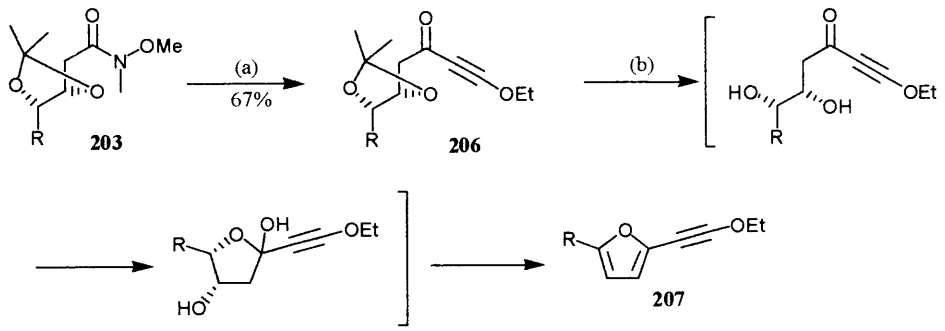
Scheme 3.20: The use of Grignard reagents to convert esters into Weinreb amides.

Acetonide protection was selected for the attempted synthesis of the natural product as this was expected to be more acid-labile and therefore more readily cleaved under the cyclisation conditions (Schemes 3.21-23).

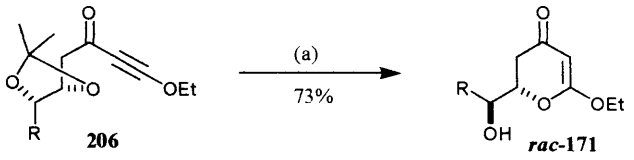


Scheme 3.21. (R = C_4H_9). *Reagents and conditions*: (a) 2,2-dimethoxypropane, acetone, *p*-TsOH (cat.), 20 °C, 2 h; (b) pent-1-ynyl-lithium, THF, 0 °C, 2 h; (c) Dowex-50, MeOH, 20°C, 48 h.

In the case of the *n*-propyl substituted intermediate **204** deprotection of the acetonide group using Dowex-50[47] resulted in the formation of the diol intermediate **205** (Scheme 3.21). However, in the case of the ethoxy-substituted compound **206**, which was needed for the synthesis of **85**, a competing cyclisation reaction occurred which resulted in the formation of the unwanted furan product **207** (Scheme 3.22). In view of this, the acetonide **206** was treated with the acidic mercury(II) solution, and this affected the one-pot cyclisation to the dihydropyran-4-one product **171** in a 75% yield (Scheme 3.23).

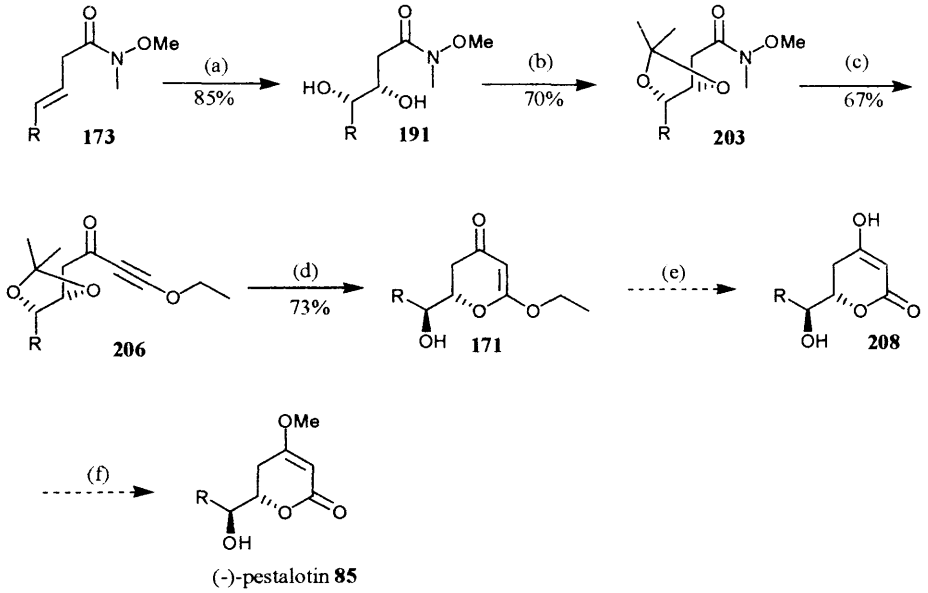


Scheme 3.22: (R = C_4H_9). *Reagents and conditions*: (a) ethoxyethynyl-lithium, THF, - 78 °C, 3 h; (b) Dowex-50, MeOH, 20°C, 48 h.



Scheme 3.23: (R = C_4H_9). *Reagents and conditions*: (a) HgO/ H_2SO_4, acetone, 20 °C, 30 min.

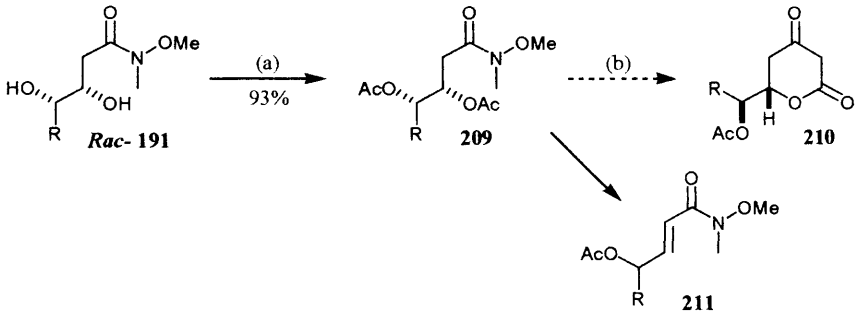
Scheme 3.24 describes the synthesis of the dihydropyranone **171** which could be converted to (-)-pestalotin by acid-mediated lactonisation followed by methylation at the 4-hydroxyl position.



Scheme 3.24: Synthesis of dihydropyranone **171** and its proposed use for the synthesis of (-)-pestalotin. *Reagents and conditions*: (a) $K_2OsO_2(OH)_4$, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, ^tBuOH-H_2O, 0 °C, 12 h; (b) 2,2-dimethoxypropane, acetone, *p*-TsOH (cat.), 20 °C, 2 h; (c) ethoxyethynyl-lithium, THF, - 78 °C, 3 h; (d) HgO/ H_2SO_4, acetone, 20 °C, 30 min; (e) HCl, 20 °C, 4 h; (f) $MeSO_4$.

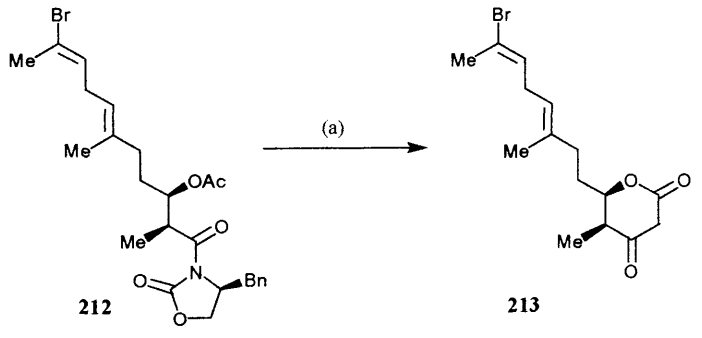
3.3.3 Attempted Synthesis of β-Ketolactone by Base-Catalysed Cyclisation

Scheme 3.25 shows the attempted synthesis of the lactone **210** using base-catalysed cyclisation; the lactone **210** may be used to synthesise **85** by *O*-methylation followed by deprotection of the acetate group. Base-catalysed cyclisations of this type using the Evans aldol product were reported recently, see Scheme 3.26.[48,49] However, in the case of α-unsubstituted Weinreb amide **209** an elimination reaction took place, which resulted in the formation of the conjugated amide **211**.



Scheme 3.25: (R = C_4H_9). *Reagents and conditions*: (a) Ac_2O, pyridine, 20 °C, 90 min; (b) KHMDS, THF, - 78 °C, 15 min.

Vanderwal and co-workers[48] reported that the treatment of imide **212** with 4.0 equiv of potassium hexamethyldisilazide (KHMDS) at - 78 °C led to the rapid expulsion of the oxazolidinone auxiliary and generated the desired β-keto lactone **213** (Scheme 3.26).



Scheme 3.26: Claisen-like Cyclisation of Imide Acetate **212**. *Reagents and conditions*: KHMDS (4.0 equiv), THF, - 78 °C.

3.4 Conclusions

In this chapter the Sharpless asymmetric dihydroxylation reaction was used in conjunction with the mercury(II) catalysed cyclisation procedure to synthesize the 2,3-dihydropyran-*4H*-one **171**, which may be modified to give the natural product (-)-pestalotin.

Experimental

(*E*)-Oct-3-enoic acid (174).[50] Hexanal (10.0 g, 83 mmol) was slowly added to a mixture of malonic acid (26.0 g, 0.25 mol) and piperidine (6.8 mg, 0.083 mmol) in xylene (100 mL) which was heated at reflux. A Dean-Stark apparatus equipped with a gas-trap was used to observe the evolution of carbon dioxide during the reaction. When no more water was separated and CO_2 ceased to evolve (12 h) the mixture was allowed to cool to room temperature, then washed with water and the xylene evaporated. The residue was distilled under reduced pressure to give **174** (11.4 g, 96%) as a colourless liquid, b. p. 150-153 °C / 18 mmHg (lit b.p.{33} 92 °C /1.4 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (2H, m, CH=CH), 3.00 (2H, d, J = 6.1 Hz, CH_2C=O), 1.98 (2H, q, J = 6.3 Hz, CH_2C=C), 1.25 (4H, m, $2CH_2$), 0.82 (3H, t, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6 (CO_2H), 134.5 (*CH*=CHCC=O), 119.7 (CH=*CH*CC=O), 36.8 (CH_2C=O), 31.1 (CH_2C=C), 30.0 (CH_2), 21.2 (CH_2), 12.9 (CH_3).

(*E*)-Oct-3-en-1-ol (175).[50,51] A solution of (*E*)-oct-3-enoic acid (2.0 g, 14.1 mmol) in anhydrous tetrahydrofuran (30 mL) was added slowly to a solution of lithium aluminium hydride in anhydrous tetrahydrofuran (14.1 mL, 14.1 mmol, 1.0 M). The reaction was heated under reflux for 1h and then cooled to 20 °C. Water was slowly added to the cooled mixture to destroy the excess of lithium aluminium hydride (CAUTION). The ethereal layer was washed with dilute hydrochloric acid (20 mL, 0.2 M), and saturated aqueous sodium hydrogen carbonate (20 mL), and the organic layer was dried ($MgSO_4$), filtered and evaporated. Distillation of the residue at reduced pressure gave **175** (1.0 g, 55%) as a colourless oil, b. p. 55-60 °C / 9 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (1H, m, CH=CH), 5.30 (1H, m, CH=CH), 3.55 (2H, t, J = 6.4 Hz, CH_2OH), 2.20 (2H, q, J = 6.4 Hz, CH_2CH_2OH), 1.96 (2H, q, J = 7.0 Hz, CH_2C=C), 1.20 (4H, m, CH_2), 0.82 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7 (*CH*=CHCCOH), 126.1 (CH=*CH*CCOH), 62.5 (CH_2OH), 36.4 (CH_2COH), 32.7 (CH_2C=C), 32.0 (CH_2), 22.6 (CH_2), 14.3 (CH_3).

(*E*)-Oct-3-enal (172).[52] Chromium trioxide (6.7 g, 67 mmol) was added to pyridine (10.5 g, 0.13 mol) in dichloromethane (200 mL) at 20 °C. After stirring for 15 min, (*E*)-3-octenol (1.0 g, 7.8 mmol) was added and stirring was continued for 20 min. The mixture was diluted with ether (50 mL), washed with aqueous sodium hydroxide (4 x 200 mL, 1M) then with dilute hydrochloric acid (2 x 80 mL, 2M), saturated aqueous sodium hydrogen carbonate (2 x 40 mL), and lastly brine (40 mL). The solution was dried over $MgSO_4$, filtered and evaporated (bath temperature 20° C). The residue was purified by column chromatography (1:5 acetone: petroleum ether) to give **172** (0.63 g, 64%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (1H, s, CHO), 5.50 (2H, m, CH=CH), 3.03 (2H, d, J = 5.7 Hz, CH_2C=O), 2.01 (2H, q, J = 6.5 Hz, CH_2C=C), 1.26 (4H, m, CH_2), 0.83 (3H, q, J = 6.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7 (CHO), 137.4 (*CH*=CHCCHO), 119.4 (CH=*CH*CCHO), 47.7 (CH_2CHO), 32.7 (CH_2C=C), 31.7 (CH_2), 22.5 (CH_2), 14.3 (CH_3).

(*E*)-Oct-3-enoyl chloride (184a). To a solution of (*E*)-oct-3-enoic acid (2.0 g, 14.1 mmol) in dichloromethane (100 mL) cooled to 0 °C under an atmosphere of nitrogen, thionyl chloride (3.2 g, 4.0 mL, 33.6 mmol) was added dropwise with stirring. The mixture was then heated under reflux at 60 °C. Progress of the reaction was monitored by TLC; after the reaction was complete the solvent and excess thionyl chloride were evaporated to give **184a** (1.64 g, 73%) as a brown oil which was used directly in the next step; IR ν_{max} (cm^{-1}) 1801 (COCl).

Oct-3-enoic acid *N*-methoxy-*N*-methylamide (173a).[42] To a stirred solution of (*E*)-oct-3-enoyl chloride (2.0 g, 12.5 mmol) in dichloromethane (100 mL) at 0 °C under an atmosphere of nitrogen, was added *N*, *O*-dimethylhydroxylamine hydrochloride (2.14 g, 22 mmol) and pyridine (3.48 g, 3.4 mL, 44 mmol). The mixture was warmed to 20 °C and stirred for a further 3 h. Hydrochloric acid (20 mL, 2 M) was added, and the aqueous layer extracted with dichloromethane (2 x 60 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2 x 60 mL) followed by brine (60 mL). The solution was dried ($MgSO_4$), filtered and evaporated. Purification of the residue by column chromatography (2:1 petroleum ether: ether) gave **173a** (2.24 g, 97%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (2H, m, CH=CH), 3.90 (CH_3, s,

OCH_3), 3.39 (5H, s, NCH_3, $CH_2C{=}O$), 2.24 (2H, m, $CH_2C{=}C$), 1.53 (4H, m, CH_2), 1.09 (3H, t, J = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3 (C=O), 134.8 (CH=*CH*CC=O), 122.6 (*CH*=CHCC=O), 61.6 (OMe), 36.5 ($CH_2C{=}O$), 32.7 ($CH_2C{=}C$), 31.8 (CH_2), 22.6 (CH_2), 14.3 (CH_3).

Attempted preparation of tridec-8-en-4-yn-6-one (185). To a solution of pent-1-yne (0.49 g, 7.1 mmol) in tetrahydrofuran (10 mL) at –78 °C was added *n*-butyllithium (2.0 mL, 5.0 mmol, 2.5 M solution in hexanes) dropwise over 10 min. After 30 min of stirring, a solution of oct-3-enoic acid *N*-methoxy-*N*-methylamide (0.60 g, 3.2 mmol) in tetrahydrofuran (10 mL) was added dropwise. After 2 h the mixture was quenched by the addition of saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted with ether (3 x 10 mL), then dried ($MgSO_4$), filtered and evaporated. Column chromatography (5:95 ethyl acetate: petroleum ether) gave a 2:1 mixture the deconjugated **185** and the conjugated alkynone (0.30 g, 48%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (1H, m, *conjugated-CH*=CHC=O), 6.34 (1H, d, J = 15.9 Hz, *conjugated*-CH=*CH*C=O), 5.60 (2H, m, *deconjugated-CH*=*CH*CC=O), 2.81 (2H, d, J = 4.9 Hz, $CH_2C{=}O$), 2.39 (2H, m, CH_2), 2.07 (2H, m, CH_2), 1.63 (4H, m, CH_2), 1.35 (3H, m, CH_3), 1.07 (2H, m, CH_2), 0.92 (3H, t, J = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C=O), 154.2 (*conjugated-CH*=CHC=O), 137.1 (de*conjugated-CH*=CHCC=O), 130.7 (*conjugated*-CH=*CH*C=O), 122.9 (de*conjugated*-CH=*CH*CC=O), 84.9 (*C*≡CC=O), 71.5 (C≡*C*C=O), 40.8 ($CH_2C{=}O$), 32.6 ($CH_2C{=}C$), 31.7 (CH_2), 22.9 (CH_2), 22.6 (CH_2), 21.7 (CH_2), 14.3 (CH_3), 13.9 (CH_3).

(*E*)-Pent-3-enoic acid (174b).[53] To a solution of 3-pentenenitrile (15.0 g, 18 mL, 185 mmol) in dichloromethane (75 mL) at 0 °C were added the following, 30% w/v aqueous hydrogen peroxide (30.6 g, 27 mL, 0.90 mol), tetrabutylammonium iodide (0.66 g, 1.8 mmol) and 20% w/v aqueous sodium hydroxide (21.6 g, 0.54 mol). The mixture was allowed to warm to 20 °C with vigorous stirring. When the reaction was complete (TLC monitoring) the aqueous layer was separated and extracted with dichloromethane (3 x 30 mL). The aqueous layer was then acidified with dilute hydrochloric acid (3.0 M), extracted with dichloromethane (5 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give **174b**

(9.25 g, 50%) as a clear yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (2H, m, CH=CH), 2.98 (2H, d, J = 5.6 Hz, CH_2C=O), 1.64 (3H, d, J = 5.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6 (CO_2H), 130.4 (CH=*CH*C=O), 122.4 (*CH*=CHC=O), 38.0 (CH_2CO) 18.2 (CH_3).

(*E*)-Pent-3-enoyl chloride (184b).[53] To a stirred solution of (*E*)-pent-3-enoic acid (1.0 g, 10 mmol) in dichloromethane (50 mL) cooled to 0 °C under an atmosphere of nitrogen, was added thionyl chloride (3.2 g, 2 mL, 27 mmol) dropwise. The mixture was then heated under reflux at 60 °C. Progress of the reaction was monitored by TLC, after the reaction was complete the solvent and the excess thionyl chloride were evaporated to give **184b** (1.0 g, 85%) as a dark brown oil, which was used directly in the next step; IR ν_{max} (cm^{-1}) 1800 (COCl).

Pent-3-enoic acid *N*-methoxy-*N*-methylamide (173b). To a solution of (*E*)-pent-3-enoyl chloride (1.0 g, 8.5 mmol) in dichloromethane (50 mL) was added *N,O*-dimethylhydroxylamine hydrochloride (1.07 g, 11 mmol) and pyridine (1.74 g, 1.7 mL, 22 mmol) with stirring at 0 °C. The mixture was then stirred at 20 °C and progress of the reaction was monitored by TLC. On completion, aqueous hydrochloric acid (10 mL, 2 M) was added, and the aqueous layer was extracted with dichloromethane (2 x 30 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2 x 30 mL) followed by brine (30 mL). The solution was dried ($MgSO_4$), filtered and evaporated, purification by flash column chromatography (1:1 ether: petroleum ether) gave **173b** (0.86 g, 71%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 1666 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (2H, m, CH=CH), 3.62 (3H, s, OCH_3), 3.10 (5H, d, J = 6.1 Hz, NCH_3, CH_2C=O), 1.60 (3H, d, J = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C=O), 129.2 (*CH*=CHCO), 123.9 (CH=*CH*CO), 61.6 (OCH_3), 36.4 (CH_2C=O), 32.7 (NCH_3), 18.2 (CH_3); LRMS m/z (%)+EI 144 (M+H, 35%), 80 (100), 56 (35), 32 (10); HRMS calcd for $C_7H_{13}O_2N$ 144.1024 (M+H), found 143.0946.

(*E*)-Oct-3-enoic acid ethyl ester (186).[54] A solution of (*E*)-oct-3-enoic acid (1.0g, 7.05 mmol) and concentrated sulfuric acid (1 drop) in ethanol (10 mL) was heated under reflux for 3 h, after cooling to 0 °C, the mixture was treated with saturated

aqueous sodium hydrogen carbonate (6.0 mL) and extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), then dried ($MgSO_4$), filtered and evaporated. Chromatography of the residue (2:98 ethyl acetate: petroleum ether) gave **186** (0.94 g, 78%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (2H, m, CH=CH), 4.15 (2H, q, J = 7.1 Hz, CH_2O), 3.01 (2H, d, J = 4.5, CH_2C=O), 2.04 (2H, q, J = 7.0, CH_2C=C), 1.30 (4H, m, CH_2), 1.25 (3H, t, J = 7.1 Hz, CH_3), 0.88 (3H, t, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C=O), 134.8 (*CH*=CHCO), 121.5 (CH=*CH*CO), 60.5 (CH_2O), 38.2 (CH_2C=O), 32.1 (CH_2C=C), 31.3 (CH_2), 22.1 (CH_2), 14.2 (CH_3), 13.9 (CH_3).

(*S,S*)-5-Butyl-4-hydroxydihydrofuran-2-one (187).[55] To a stirred suspension of ADmix-α (12.0 g) and methanesulfonamide (0.84 g, 8.82 mmol) in a 1:1 mixture of *tert*-butyl alcohol/ water (85 mL) was added (*E*)-oct-3-enoic acid ethyl ester (1.50 g, 8.82 mmol). The mixture was stirred at 0 °C for 40 h, then quenched by the addition of ethyl acetate (45 mL) and sodium sulfite (12.9 g). After removal from the cryostat, the mixture was stirred for a further 30 min at 20 °C, extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with aqueous potassium hydroxide (2 x 30 mL, 2M) followed by brine (2 x 30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash column chromatography (4:6 ethyl acetate: petroleum ether) gave **187** (0.91 g, 65%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (1H, m, *CH*OH), 4.35 (1H, m, *CH*OH), 2.80 (1H, dd, J = 17.5 and 5.4 Hz, CH_2C=O), 2.56 (1H, d, J = 17.5 Hz, CH_2C=O), 1.84 (2H, m, CH_2COH), 1.40 (4H, m, CH_2), 0.92 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1 (C=O), 85.1 (O*CH*), 69.0 (*CH*OH), 39.5 (CH_2C=O), 27.9 (CH_2), 27.7 (CH_2), 22.5 (CH_2), 13.9 (CH_3).

3,4-Dihydroxyoctanoic acid ethyl ester (188). To a solution of *N*-methylmorpholine *N*-oxide (10.7 g, 79.4 mmol) in water (5.8 mL) was added, in succession, potassium osmate dihydrate (0.78 g, 2.12 mmol) and (*E*)-oct-3-enoic acid ethyl ester (9.0 g, 52.9 mmol) dissolved in acetone (30.0 mL). The mixture was stirred at 20 °C and monitored by TLC until the reaction was complete (24 h). Saturated aqueous sodium hydrosulfite (13.5 mL) was added and the mixture stirred for 30 min, then it was filtered through celite and rinsed with acetone, evaporation of

the solvent and column chromatography (4:6 ethyl acetate: petroleum ether) gave **188** (8.5 g, 79%) as a white solid; IR ν_{max} (cm^{-1}) 3457 (OH), 1682 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (2H, q, *J* = 7.1 Hz, *CH*$_2$O), 3.86 (1H, m, OCH), 3.42 (1H, m, OCH), 2.52 (2H, m, CH_2C=O), 1.47 (2H, m, CH_2COH), 1.33 (4H, m, CH_2), 1.23 (3H, t, *J* = 7.1 Hz, CH_3), 0.88 (3H, t, *J* = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C=O), 73.7 (*CH*OH), 70.5 (*CH*OH), 60.8 (CH_2O), 38.3 (*CH*$_2$CO), 33.1 (CH_2), 27.8 (CH_2), 24.0 (CH_3), 22.6 (CH_2), 14.1 (CH_3); LRMS m/z (%)+FAB 205 (M+H, 10%), 159 (100), 143 (20); HRMS calcd for $C_{10}H_{20}O_4$ 205.1440 (M+H), found 205.1446.

5-Butyl-4-hydroxydihydrofuran-2-one (*rac*-187a).[55] A stirred mixture of 3,4-dihydroxyoctanoic acid ethyl ester (4.0 g, 19.6 mmol) and *p*-toluenesulfonic acid (0.16 g, 0.86 mmol) in benzene (200 mL) was heated at 50 °C for 90 min. The mixture was cooled and neutralized by the addition of pyridine. Evaporation and column chromatography (4:6 ethyl acetate: petroleum ether) of the residue gave **187a** (3.39 g, 87%) as an orange oil. The spectroscopic data were identical to those given for **187**.

5-Butyl-4-(trimethylsilanyloxy)-dihydrofuran-2-one (189). Triethylamine (1.84 g, 18.2 mmol) and chlorotrimethylsilane (1.90 g, 17.4 mmol) were added simultaneously to a stirred solution of 5-butyl-4-hydroxydihydrofuran-2-one (2.5 g, 15.8 mmol) in anhydrous ether (20 mL) at 0 °C. The solution was then stirred at 20 °C for 12 h. Pentane (20 ml) was then added and the resulting slurry stirred for 10 min. Filtration and evaporation gave a residue which was purified by flash column chromatography (1:9 ethyl acetate: petroleum ether) to give **189** (2.0 g, 90%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 1732 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (1H, m, OCH), 4.31 (1H, m, *CH*OTMS), 2.72 (1H, dd, *J* = 17.2 and 5.2 Hz, CH_2C=O), 2.44 (1H, d, *J* = 17.2 Hz, CH_2C=O), 1.62 (2H, m, CH_2), 1.38 (4H, m, CH_2), 0.91 (3H, t, *J* = 6.7 Hz, CH_3) 0.12 (18H, s, Si(*CH*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7 (C=O), 85.1 (OCH), 69.3 (*CH*OTMS), 39.8 (*CH*$_2$CO), 28.2 (CH_2), 27.5 (CH_2), 22.6 (CH_2), 13.9 (CH_3), - 0.10 (Si*CH*$_3$); LRMS m/z (%)+EI 231 (M+H, 15%), 190 (40), 159 (75), 147 (20), 116 (40), 95 (20), 73 (100), 59 (10); HRMS calcd for $C_{11}H_{22}O_3Si$ 231.1416 (M+H), found 231.1414.

Attempted preparation of 1-ethoxy-6-hydroxy-5-(trimethylsilanyloxy)-dec-1-yn-3-one. To a stirred solution of 5-butyl-4-(trimethylsilanyloxy)-dihydrofuran-2-one (0.70 g, 3.04 mmol) in tetrahydrofuran (15 mL) was added a solution of lithium ethoxyacetylide (prepared by the addition of *n*-butyllithium (2.2 mL, 5.48 mmol, 2.5 M solution in hexanes) to a stirred solution of ethoxyacetylene (0.43 g, 0.6 mL, 6.09 mmol, 50% solution in hexanes) in tetrahydrofuran (15 mL) at – 78 °C followed by stirring for 30 min). After a further 2 h the mixture was quenched by the addition of saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted with ether (3 x 10 mL), dried and evaporated. Column chromatography (10:90 ethyl acetate: petroleum ether) gave the by-product **190** (0.30 g, 62%) as pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, m, *CH*=CHC=O), 6.02 (1H, d, *J* = 15.3 Hz, CH=*CH*C=O), 4.50 (1H, m, O*CH*), 1.48 (2H, m, CH_2), 1.32 (2H, m, CH_2), 1.22 (2H, m, CH_2), 0.98 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C=O), 147.1 (*CH*=CHC=O), 121.1 (CH=*CH*C=O), 80.4 (OCH), 33.7 (CH_2), 26.3 (CH_2), 22.3 (CH_2), 13.7 (CH_3).

3,4-Dihydroxyoctanoic acid *N*-methoxy-*N*-methylamide (*rac*-191).[42] To a solution of *N*-methylmorpholine *N*-oxide (0.55 g, 4.0 mmol) in water (0.30 mL) was added, in succession, potassium osmate dihydrate (0.04 g, 0.11 mmol) and (*E*)-oct-3-enoic acid *N*-methoxy-*N*-methylamide (0.50 g, 2.7 mmol) dissolved in acetone (1.5 mL). The solution was stirred at 20 °C and monitored by TLC until complete (24 h). Saturated aqueous sodium hydrosulfite (0.35 mL) was added and the mixture stirred for 30 min, filtered through celite and the celite rinsed with acetone. The combined filtrates were evaporated and the residue subjected to chromatography (5:95 methanol: dichloromethane) to give ***rac*-191** (0.45 g, 76%) as a brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (1H, m, *CH*OH), 3.63 (3H, s, OMe), 3.39 (1H, m, *CH*OH), 3.13 (3H, s, NMe), 2.60 (2H, d, *J* = 7.6 Hz, CH_2C=O), 2.40 (1H, bs, OH), 1.64 (1H, bs, OH), 1.46 (2H, m, CH_2COH), 1.28 (4H, m, CH_2), 0.84 (3H, t, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C=O), 74.3 (COH), 70.8 (COH), 61.7 (OCH_3), 35.4 (CH_2), 33.7 (CH_2CO), 31.2 (NCH_3), 28.3 (CH_2), 23.1 (CH_2), 14.4 (CH_3).

(*3S,4S*)-3,4-Dihydroxyoctanoic acid *N*-methoxy-*N*-methylamide (191a).[42] A mixture of the chiral ligand $(DHQ)_2$-PHAL (38.9 mg, 5.0 x 10^{-5} mol), potassium ferricyanide (0.99 g, 3.0 mmol), potassium carbonate (0.42 g, 3.0 mmol), potassium osmate (3.68 mg, 1.0 x 10^{-5} mol) and methanesulfonamide (95 mg, 1.0 mmol) were dissolved in a 1:1 mixture of water and *tert*-butyl alcohol (10 mL) at 0 °C. (*E*)-Oct-3-enoic acid *N*-methoxy-*N*-methylamide (0.185 g, 1.0 mmol) was added in one portion and the mixture was stirred at 0 °C for 12 h, then quenched by the addition of sodium sulfite (1.5 g) followed by warming to 20 °C and stirred for a further 30 min. The mixture was extracted with dichloromethane (3 x 6 mL) and the combined organic layers were washed with aqueous potassium hydroxide (2 x 10 mL, 2M) and then dried (Na_2SO_4), filtered and evaporated to give a mixture of the crude diol and the ligand. Purification by flash column chromatography (90:10 ethyl acetate: petroleum ether) gave **191a** (0.18 g, 85%) as a pale yellow oil, the spectroscopic data are identical to those for the racemic compound.

3,4-Bis-(trimethylsilanyloxy)-octanoic acid *N*-methoxy-*N*-methylamide (192). Triethylamine (1.6 g, 15.7 mmol) and chlorotrimethylsilane (1.6 g, 15.1 mmol) were added simultaneously to a stirred solution of (*3S,4S*)-3,4-dihydroxyoctanoic acid *N*-methoxy-*N*-methylamide (1.50 g, 6.8 mmol) in dry ether (14 mL) at 0 °C. The solution was then stirred at 20 °C for 12 h. Pentane (14 ml) was then added and the resulting slurry stirred for 10 min. Filtration and evaporation gave a residue which was purified by flash column chromatography (1:4 ethyl acetate in hexane) to give **192** (2.0 g, 80%) as a light brown oil; IR ν_{max} (cm^{-1}) 1673 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (1H, m, OCH), 3.68 (3H, s, OMe), 3.58 (1H, m, OCH), 3.17 (3H, s, NMe), 2.54 (2H, m, CH_2CO), 1.29 (6H, m, $3CH_2$), 0.90 (3H, t, J = 7.1, CH_3), 0.08 (18 H, s, $2Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.0 (*OCH*), 71.9 (*OCH*), 61.2 (OCH_3), 33.9 (NCH_3), 30.4 ($2CH_2$), 28.6 (CH_2), 22.7 (CH_2), 14.0 (CH_3), 0.40 ($Si(CH_3)_3$); LRMS m/z (%)+Cl 363 (M^+, 5%), 271 (25), 212 (25), 211 (100), 156 (35), 137 (58), 85 (15); HRMS calcd for $C_{16}H_{37}NO_4Si_2$ 363.2261 (M+H), found 363.2240.

1-Ethoxy-5,6-bis-(trimethylsilanyloxy)-dec-1-yn-3-one (193). To a solution of ethoxyacetylene (1.15 g, 8.20 mmol, 50% solution in hexanes) in tetrahydrofuran (20 mL) was added *n*-butyllithium (2.95 mL, 7.40 mmol, 2.5 M solution in hexanes) dropwise over 10 min at –78 °C. After 30 min of stirring, a solution of 3,4-bis-trimethylsilanyloxyoctanoic acid *N*-methoxy-*N*-methylamide (1.0 g, 2.73 mmol) in tetrahydrofuran (20 mL) was added in one portion. After 3 h the mixture was quenched by addition of saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted with ether (3 x 10 mL), dried and evaporated. Column chromatography (10:90 ethyl acetate: petroleum ether) gave **193** (0.67 g, 60%) as a yellow oil; IR ν_{max} (cm^{-1}) 2211 (alkyne), 1696 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (3H, q, J = 7.1 Hz, CH_2O and OCH), 3.55 (1H, m, OCH), 2.63 (2H, m, CH_2C=O), 1.27 (9H, m, $3CH_2$ and CH_3), 0.90 (3H, t, J = 7.0 Hz, CH_3), 0.10 (18 H, s, $2Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0 (C=O), 74.6 (OCH), 71.5 (OCH), 61.2 (CH_2O), 44.4 (CH_2C=O), 29.9 (CH_2), 28.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 14.0 (CH_3), 0.2 ($Si(CH_3)_3$).

Attempted preparation of 1-ethoxy-5,6-dihydroxydec-1-yn-3-one (170). Tetra-butylammonium fluoride (1.4 mL, 4.8 mmol, 1.0 M solution in tetrahydrofuran) was added to a solution of 1-ethoxy-5,6-bis-(trimethylsilanyloxy)-dec-1-yn-3-one (1.0 g, 2.4 mmol) in tetrahydrofuran (10 mL). The mixture was stirred at 20 °C for 2 h, then water (30 mL) and ethyl acetate (60 mL) were added. The separated organic layer was washed with brine (30 mL) and the combined aqueous layers were extracted with ethyl acetate (3 x 40 mL). The organic layers were dried ($MgSO_4$), filtered and evaporated to give a mixture of products as shown by ^{1}H NMR.

3-(*tert*-Butyldimethylsilanyloxy)-butyric acid ethyl ester (195).[56] Imidazole (2.06 g, 30.2 mmol) and *tert*-butyldimethylsilyl chloride (2.74 g, 18.2 mmol) were added consecutively to a stirred solution of the 3-hydroxybutyric acid ethyl ester (2.0 g, 15.2 mmol) in dry dichloromethane (120 mL) at 20 °C. After 3 h, water (60 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography (1:99, ethyl acetate:

hexane) gave **195** (3.0 g, 80%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (1H, m, OCH), 4.09 (2H, q, J = 7.2 Hz, CH_2O), 2.46 (1H, dd, J = 14.5 and 7.5 Hz, CH_2C=O), 2.35 (1H, dd, J = 14.5, 5.4 Hz, CH_2C=O), 1.23 (3H, t, J = 7.2 Hz, CH_3), 1.18 (3H, d, J = 6.1 Hz, CH_3), 0.84 (9H, s, $(CH_3)_3CSi(CH_3)_2$), 0.02 (6H, s, $(CH_3)_3CSi(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (C=O), 65.8 (OCH), 60.2 (CH_2O), 44.9 (CH_2), 25.7 $(CH_3)3CSi(CH_3)_2$), 23.9 (CH_3), 17.9 $(CH_3)_3CSi(CH_3)_2$), 14.2 (CH_3), - 4.5 $(CH_3)_3CSi(CH_3)_2$).

3-(*tert*-Butyldimethylsilanyloxy)-*N*-methoxy-*N*-methylbutyramide (196).[57] To a solution of 3-(*tert*-butyldimethylsilanyloxy)-butyric acid ethyl ester (0.30 g, 1.21 mmol) and *N, O*-dimethylhydroxylamine hydrochloride (0.18 g, 1.88 mmol) in ether (2.5 mL) at - 20 °C, was added a solution of isopropylmagnesium chloride (prepared *in situ* by the slow addition of isopropyl chloride (0.28 g, 3.64 mmol) to magnesium turnings (0.088 g, 3.64 mmol) in ether (2.0 mL) and heated under reflux for 2 h) the mixture was stirred for a further 20 min and quenched by the addition of aqueous ammonium chloride (4.0 mL, 20 wt %). The product was extracted with *tert*-butyl methyl ether (3 x 4.0 mL) and the organic layers were dried ($MgSO_4$), filtered and evaporated. Column chromatography (20:80 ethyl acetate: petroleum ether) gave **196** (0.26 g, 83%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (1H, sextet, J = 6.0 Hz, O*CH*), 3.69 (3H, s, CH_3O), 3.16 (3H, s, CH_3N), 2.76 (1H, dd, J = 14.4, 7.4 Hz, CH_2CO), 2.35 (1H, dd, J = 14.4, 6.0 Hz, CH_2CO), 1.21 (3H, d, J = 7.4 Hz, CH_3), 0.86 (9H, s, $(CH_3)_3CSi(CH_3)_2$), 0.06 (6H, s, $(CH_3)_3CSi(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.0 (O*CH*), 61.3 (CH_3O), 41.8 (CH_3N), 25.8 ($(CH_3)_3CSi$), 24.2 (CH_2), 18.0 (CH_3), - 4.7 ($Si(CH_3)_2$).

2-(*tert*-Butyldimethylsilanyloxy)-non-5-yn-4-one (197). *n*-Butyllithium (5.0 mL, 12.5 mmol, 2.5 M in hexane) was added dropwise to a solution of pent-1-yne (0.94 g mL, 13.8 mmol) in tetrahydrofuran (10 mL) cooled to – 78 °C under an atmosphere of nitrogen. Stirring was continued for 10 min at – 78 °C, then the mixture was treated dropwise with a solution of 3-(*tert*-butyldimethylsilanyloxy)-*N*-methoxy-*N*-methylbutyramide (1.20 g, 4.61 mmol) in tetrahydrofuran (10 mL). The stirred mixture was allowed to warm to 0 °C and stirred for a further 2 h. The mixture was then poured into saturated aqueous ammonium carbonate (10 mL) and the separated

aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. Flash chromatography (5:95 ethyl acetate: petroleum ether) gave **197** (0.70 g, 57%) as a pale yellow oil; IR ν_{max} (cm^{-1}) 2218 (alkyne group), 1691 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (1H, m, CHOTBS), 2.75 (1H, dd, *J* = 14.8, 7.3 Hz, CH_2C=O), 2.56 (1H, dd, *J* = 14.8, 5.5 Hz, CH_2C=O), 2.33 (2H, t, *J* = 7.0 Hz, $CH_2C{\equiv}C$), 1.61 (2H, sextet, *J* = 7.0 Hz, CH_2), 1.20 (3H, d, *J* = 6.1 Hz, *CH*$_3$CHO), 1.01 (3H, t, *J* = 7.0 Hz, *CH*$_3$$CH_2$), 0.85 (9H, s, Si(*CH*$_3$)$_3$), 0.04 (6H, s, 2Si*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3 (C=O), 94.3 (*C*≡CC=O), 81.6 (C≡*C*C=O), 65.5 (OCH), 55.4 (CH_2C=O), 25.8 (Si*C*(*CH*$_3$)$_3$), 24.0 (CH_2), 21.2 (CH_2), 21.0 (CH_3), 18.0 (Si*C*(CH_3)$_3$), 13.5 (CH_3), - 4.5 (Si*CH*$_3$), - 5.0 (Si*CH*$_3$); LRMS m/z (%)+FAB 269 (M+H, 50%), 253 (10), 211 (100), 159 (87); HRMS calcd for $C_{15}H_{28}O_2Si$ 269.1937 (M+H), found 269.1845.

2-Methyl-6-propyl-2,3-dihydropyran-4-one (198). To a stirred solution of 2-(*tert*-butyldimethylsilanyloxy)-non-5-yn-4-one (0.30 g, 1.12 mmol) in acetone (30 mL, HPLC grade) at 20 °C was added acidified mercury(II) sulfate solution (0.30 mL, 0.1 M HgO in 2.5 % H_2SO_4). The mixture was stirred for 6 h then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was dissolved in ether (20 mL) and the solution we washed with water (20 mL). The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (30 mL), then brine (30 mL), and the organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (30:70 ethyl acetate: petroleum ether) to give **198** (0.12 g, 75%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (1H, s, *CH*=C), 4.45 (1H, m, O*CH*), 2.35 (2H, d, *J* = 7.0 Hz, *CH*$_2$CO), 2.19 (2H, t, *J* = 7.5 Hz, CH_2), 1.58 (2H, sextet, *J* = 7.5 Hz, CH_2), 1.44 (3H, d, *J* = 6.4 Hz, CH_3), 0.93 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1 (C=O), 177.6 (*C*=CH), 104.0 (*CH*=C), 75.5 (O*CH*), 42.7 (*CH*$_2$C=O), 36.7 (CH_2), 20.4 (CH_3), 19.7 (CH_2), 13.5 (CH_3).

2-(5-Butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-*N*-methoxy-*N*-methylacetamide (203). 3,4-Dihydroxyoctanoic acid *N*-methoxy-*N*-methylamide (0.20 g, 0.91 mmol) was dissolved in a mixture of 2,2-dimethoxypropane and acetone (1:1, 9.0 mL) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (8.7 mg, 4.5 x 10^{-5} mol) was added. The mixture was stirred at 20 °C until completion (approx. 2 h). Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture which was then extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (1:4 ethyl acetate: petroleum ether) to give **203** (0.16 g, 70%) as a brown oil; IR ν_{max} (cm^{-1}) 1688 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$ δ 4.29 (1H, m, OCH), 3.86 (4H, m, OCH, CH_3O), 3.34 (3H, s, NCH_3), 2.99 (1H, dd, *J* = 15.1, 7.6 Hz, CH_2C=O), 2.69 (1H, dd, *J* = 15.1, 4.3 Hz, CH_2C=O), 1.74-1.53 (12H, m, $3CH_2$, $2CH_3$), 1.05 (3H, t, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.0 (C=O), 108.7 ($C(CH_3)_2$), 81.3 (O*CH*), 77.4 (O*CH*), 61.7 (OCH_3), 36.2 (CH_2C=O), 32.7 (CH_2), 31.2 (NCH_3), 28.5 (CH_2), 27.8 (CH_3), 27.7 (CH_3), 23.1 (CH_2), 14.3 (CH_3); LRMS m/z (%)+EI 260 (27%), 244 (10), 202 (70), 184 (30), 141 (10), 59 (8), 43 (10); HRMS calcd for $C_{13}H_{25}O_4N$ 260.1861, found 260.1860.

1-(5-Butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-hept-3-yn-2-one (204). A solution of pent-1-yne (0.57 mL, 5.8 mmol) in tetrahydrofuran (20 mL) was cooled to – 78 °C under a nitrogen atmosphere, *n*-butyllithium (3.4 mL, 3.86 mmol, 2.5 M in hexane) was added and stirring was continued for 10 min at – 78 °C. The mixture was then treated dropwise with a solution of 2-(5-butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-*N*-methoxy-*N*-methylacetamide (1.0 g, 3.86 mmol) in tetrahydrofuran (10 mL), after which the mixture was allowed to warm to 0 °C and stirred for 2 h. The mixture was poured onto saturated ammonium carbonate (10 mL) and the separated aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. Flash chromatography gave **204** (0.35 g, 34%) as an orange oil, IR ν_{max} (cm^{-1}) 2212 (alkyne group), 1682 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (1H, m, OCH), 3.62 (1H, q, *J* = 7.4 Hz, OCH), 2.75 (1H, dd, *J* = 15.8, 7.7 Hz, CH_2C=O), 2.67 (1H, dd, *J* = 15.8, 4.4 Hz, CH*H*C=O), 2.28 (2H, t, *J* = 7.3 Hz, CH_2C≡C), 1.54 (4H, m, CH_2), 1.33 (10H, m, $2CH_2$ and $2CH_3$), 0.95 (3H, t, *J* = 7.3 Hz, CH_3), 0.84 (3H, t, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz,$CDCl_3$) δ 185.0

(C=O), 109.0 (CMe_2), 95.9 (*C*≡CC=O), 81.5 (C≡*C*C=O), 81.1 (OCH), 76.7 (OCH), 49.4 (CH_2C=O), 32.6 (CH_2), 28.5 (CH_2), 27.7 (CH_3), 27.5 (CH_3), 23.1 (CH_2), 21.6 (CH_2), 21.3 (CH_2), 14.3 (CH_3), 13.8 (CH_3); LRMS m/z (%)+FAB 267 (M+H, 5%), 265 (12), 251 (25), 209 (75), 191 (100), 157 (15), 95 (50), 85 (15), 59 (25); HRMS calcd for $C_{16}H_{26}O_3$ 267.1960 (M+H), found 267.1962.

8,9-Dihydroxytridec-4-yn-6-one (205). To a solution of 1-(5-butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-hept-3-yn-2-one (0.20 g, 0.75 mmol) in methanol (25 mL) was added Dowex-50 (5.0 g) and the mixture was stirred at 20 °C for 48 h. The resin was removed by filtration and washed with methanol. Evaporation of the combined filtrates gave a residue that was purified by flash column chromatography (1:1 ethyl acetate: petroleum ether) to give **205** (0.10 g, 59%) as an orange oil; IR ν_{max} (cm^{-1}) 3417 (OH), 2214 (alkyne group), 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (1H, m, CHOH), 3.89 (1H, m, CHOH), 2.35 (2H, t, J = 7.0 Hz, CH_2C≡C), 1.59 (4H, m, CH_2COH, CH_2C=O), 1.29 (6H, m, $3CH_2$), 0.97 (3H, t, J = 7.3 Hz, CH_3), 0.85 (3H, t, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1 (C=O), 101.1 (*C*≡CC=O), 80.9 (COH), 78.5 (C≡*C*C=O), 72.3 (COH), 38.0 (CH_2C=O), 34.8 (CH_2COH), 32.0 (CH_2), 25.8 (CH_2), 22.9 (CH_2), 21.5 (CH_2), 14.3 (CH_3), 13.8 (CH_3); LRMS m/z (%)+EI 227 (M+H, 6%), 224 (40), 209 (100), 187 (20), 179 (25), 165 (80), 149 (25); HRMS calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1559.

1-(5-Butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-4-ethoxybut-3-yn-2-one (206). A solution of ethoxyacetylene (1.13 mL, 5.8 mmol) in tetrahydrofuran (20 mL) was cooled to – 78 °C under an atmosphere of nitrogen, *n*-butyllithium (2.1 mL, 5.2 mmol, 2.5 M in hexane) was added and stirring was continued for 10 min at – 78 °C. A solution of 2-(5-butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-*N*-methoxy-*N*-methyl acetamide (0.50 g, 1.93 mmol) in tetrahydrofuran (20 mL) was then added dropwise and the mixture was allowed to warm to 0 °C and stirred for 3 h. The mixture was poured onto saturated aqueous ammonium chloride (10 mL) and the separated aqueous layer was extracted with ether (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. Flash chromatography (2:8 ethyl acetate: petroleum ether) gave **206** (0.35 g, 67%) as an orange oil; IR ν_{max} (cm^{-1}) 2222 (alkyne group), 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (2H, q, J =

7.0 Hz, CH_2O), 3.91 (1H, m, O*CH*), 3.57 (1H, m, O*CH*), 2.66 (2H, m, CH_2C=O), 1.49 (2H, m, CH_2), 1.31 (13H, m, $2CH_2$ and $3CH_3$), 0.86 (3H, t, J = 6.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9 (C=O), 109.0 (CMe_2), 91.0 (C≡CC=O), 81.3 (C≡CC=O), 81.2 (OCH), 76.8 (OCH), 61.7 (CH_2O), 46.5 (CH_2C=O), 32.5 (CH_2), 28.5 (CH_2), 27.7 (CH_3), 27.5 (CH_3), 23.1 (CH_2), 14.5 (CH_3), 14.2 (CH_3); LRMS m/z (%)+FAB 307 (20), 287 (18), 271 (10), 257 (5), 239 (8), 229 (30), 211 (60), 183 (12), 154 (100); HRMS calcd for $C_{15}H_{24}O_4$ 268.1909, found 268.1895.

Attempted preparation of 1-ethoxy-5,6-dihydroxydec-1-yn-3-one (170). To a solution of 1-(5-butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-4-ethoxybut-3-yn-2-one (0.30 g, 1.11 mmol) in methanol (25 mL) was added Dowex-50 (3.0 g) and the mixture was stirred at 20 °C for 48 h. The resin was then removed by filtration and washed with methanol. Evaporation of the combined filtrates gave a residue that was purified by flash column chromatography (10:90 diethyl ether: petroleum ether) to give the by-product 2-butyl-5-ethoxyethynylfuran **207** (0.15 g, 70%) as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (1H, d, J =3.0 Hz, *CH*=C), 5.83 (1H, d, J =3.0 Hz, *CH*=C), 4.12 (2H, q, J = 7.1 Hz, CH_2O), 2.51 (2H, t, J = 7.3 Hz, CH_2), 1.50 (2H, m, CH_2), 1.28 (2H, m, CH_2), 1.19 (3H, t, J = 7.1 Hz, CH_3), 0.85 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0 (CH_2C=CH), 146.2 (C≡*CC*=CH), 108.7 (*CH*=CC≡*C*), 105.8 (*CH*=CCH_2), 82.5 (C≡*C*O), 61.4 (CH_2O), 31.7 (CH_2), 30.5 (CH_2), 28.1 (CH_2), 22.6 (*C*≡CO), 14.5 (CH_3), 14.1 (CH_3).

6-Ethoxy-2-(1-hydroxy-pentyl)-2,3-dihydropyran-4-one (*rac*-171). To a stirred solution of 1-(5-butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-4-ethoxybut-3-yn-2-one (0.30 g, 1.12 mmol) in acetone (30 mL, HPLC grade) at 20 °C was added acidified mercury(II) sulfate solution (0.30 mL, 0.1 M HgO in 2.5 % H_2SO_4). The mixture was stirred for 30 min then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, and then worked up as for **198**. The residue was purified by flash column chromatography on silica gel (3:7 ethyl acetate: petroleum ether) to give ***rac*-171** (0.19 g, 73%) as a yellow oil; IR ν_{max} (cm^{-1}) 3482 (OH), 1695 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (1H, s, *CH*=C), 3.79 (3H, m, CH_2O, O*CH*), 3.44 (1H, m, *CH*OH), 2.32 (1H, dd, J = 14.4, 7.7 Hz, C*H*HC=O), 2.25 (1H, dd, J = 14.4, 4.5 Hz, CH*H*C=O), 1.14 (9H, m, CH_3, $3CH_2$),

0.65 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7 (C=O), 169.0 (*C*=CH), 108.4 (*CH*=C), 81.3 (OCH), 78.3 (*CH*OH), 64.2 (CH_2O), 32.7 (CH_2CO), 28.8 (CH_2), 27.7 (CH_2), 23.1 (CH_2), 14.6 (CH_3), 14.2 (CH_3); LRMS m/z (%)+CI 229 (M+H, 60%), 211 (90), 183 (80), 157 (70), 141 (100), 123 (50); HRMS calcd for $C_{12}H_{20}O_4$ 229.1440 (M+H), found 229.1437.

2-Acetoxy-1-[(methoxy-methyl-carbamoyl)-methyl]-hexyl acetate (209). To a stirred solution of 3,4-dihydroxyoctanoic acid *N*-methoxy-*N*-methylamide (0.20 g, 0.91 mmol) in pyridine (2.0 mL, 24.8 mmol) at 0 °C was added acetic anhydride (2.0 mL, 1.82 mmol). After stirring for 90 min, the solvents were evaporated and the residue was purified by column chromatography (3:7 ethyl acetate: petroleum ether) to give **209** (0.26 g, 93%) as a colourless oil; IR ν_{max} (cm^{-1}) 1693 (C=O), 1652 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (1H, m, O*CH*), 5.09 (1H, m, O*CH*), 3.66 (3H, s, CH_3O), 3.14 (3H, s, CH_3N), 2.65 (2H, d, J = 5.9 Hz, CH_2C=O), 2.07 (3H, s, CH_3C=O), 2.05 (3H, s, CH_3C=O), 1.56 (2H, q, J = 7.4 Hz, CH_2), 1.27 (4H, m, CH_2), 0.86 (3H, t, J = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C=O), 170.1 (C=O), 73.7 (OCH), 70.2 (OCH), 61.2 (CH_3O), 33.6 (CH_2C=O), 32.2 (CH_3N), 30.3 (CH_2), 27.4 (CH_2), 22.4 (CH_2), 21.0 (CH_3C=O), 20.9 (CH_3C=O), 13.9 (CH_3); LRMS m/z (%)+EI 304 (M+H, 100%), 244 (100), 215 (20), 202 (100), 184 (70), 173 (85), 141 (90), 132 (100), 123 (83), 113 (35), 99 (100), 81 (90), 69 (42); HRMS calcd for $C_{14}H_{25}O_6N$ 303.1682, found 303.1685.

Attempted synthesis of 1-(4,6-dioxotetrahydropyran-2-yl)-pentyl acetate (210). 2-Acetoxy-1-[(methoxy-methyl-carbamoyl)-methyl]-hexyl acetate (0.20 g, 0.66 mmol) was dissolved in tetrahydrofuran (6.0 mL) and cooled to – 78 °C. KHMDS (1.32 mL, 1.32 mmol, 1.0 M in tetrahydrofuran) was added over 5 min, and after a further 10 min the mixture was quenched by the rapid addition of aqueous hydrochloric acid (6.0 mL, 0.5 M). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give after column chromatography (7:3 ethyl acetate: petroleum ether) the amide by-product **211** (0.10 g, 62%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (1H, dd, J = 15.5, 6.1 Hz, *CH*=CHC=O), 6.55 (1H, d, J = 15.5 Hz, CH=*CH*C=O), 5.40 (1H, q, J = 6.1 Hz, O*CH*), 3.69 (3H, s, OCH_3), 3.24 (3H, s,

NCH_3), 2.08 (3H, s, $CO\mathit{CH_3}$), 1.62 (2H, m, CH_2), 1.32 (4H, m, CH_2), 0.88 (3H, t, J = 6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2 ($CH_3O\mathit{C}$=O), 162.4 (C=O), 147.9 (*CH*=CHC=O), 120.5 (CH=*CH*C=O), 78.1 (OCH), 52.8 (CH_3O), 34.0 (CH_3N), 33.6 (CH_2), 27.5 (CH_2), 23.9 (CH_2), 18.2 ($CO_2\mathit{CH_3}$), 14.3 (CH_3).

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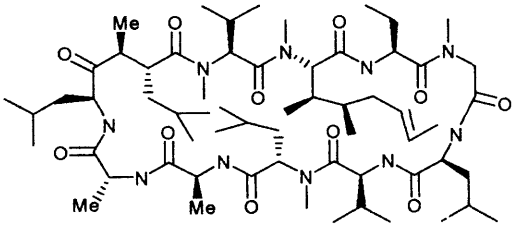
Chapter 4

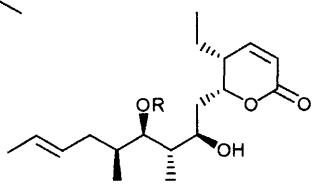
Towards the Total Synthesis of NK10958P

4.1 Introduction

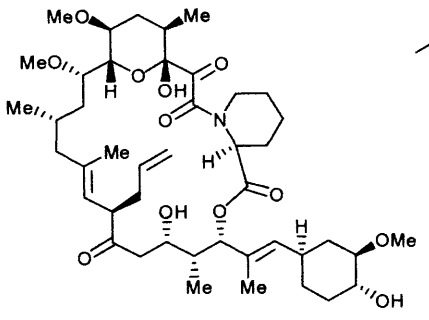
Natural products possessing immunosuppressant activity have received a great deal of attention since the introduction of cyclosporin A (CsA)[1] **214** and FK-506[2] **215**, which are used for the treatment of autoimmune diseases, especially those associated with organ transplantation.[3] Recently Kawada and co-workers reported the isolation of the novel immunosuppressant agent **84** (PA-48153C)[4] from the fermentation broths of *Streptomyces prunicolor* PA-48153C and found it to possess potent immunosuppressant activity similar to that exhibited by **214** and **215**. Interestingly, PA-48153C **84** was found to have a different mode of action to CsA **214** and FK-506 **215**; PA-48153C was found to inhibit the responses of both T and B lymphocytes to mitogens, [5] while CsA and FK-506 affect only T-cell activation.[6] Kobayashi and co-workers have also reported the isolation of a plant-growth regulator, given the name pironetin, from *Streptomyces sp.* NK10958P whose structure has proven to be identical with that of **84** (Figure 4.1).[7]



Cyclosporin A **214**



R = H, NK10958P **83**
R = Me, Pironetin **84**



FK-506 **215**

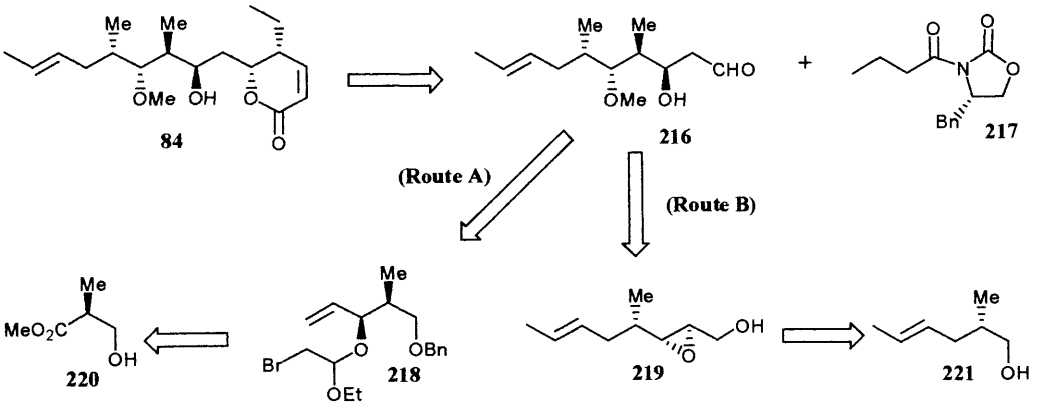
Figure 4.1: The structures of CsA, FK-506 and pironetin.

A major limitation to pironetin as a therapeutic agent is its high cytotoxicity; however, recently certain structurally-modified derivatives of pironetin have shown promise.[8] Moreover, these relatively simple structures exhibit potency comparable to that shown by CsA. Another recent report in the literature suggests efficacy of certain derivatives of **84** in assays against uterine and ovarian tumours, in addition to activity as inhibitors of tubulin polymerisation and thus the cell cycle.[6,9]

4.2 Syntheses of Pironetin Reported in the Literature

Interesting biological activity and a simple structure makes **84** and its demethylated analogue **83** attractive synthetic targets. In 1995, the first total synthesis of **84** was reported by Kawada and co-workers,[10] which utilized a carbohydrate approach to the 2-pyranone ring. Since then more than four total syntheses of **84** have been reported, [6,11-13] those generally involve over 20 steps with complex starting material.

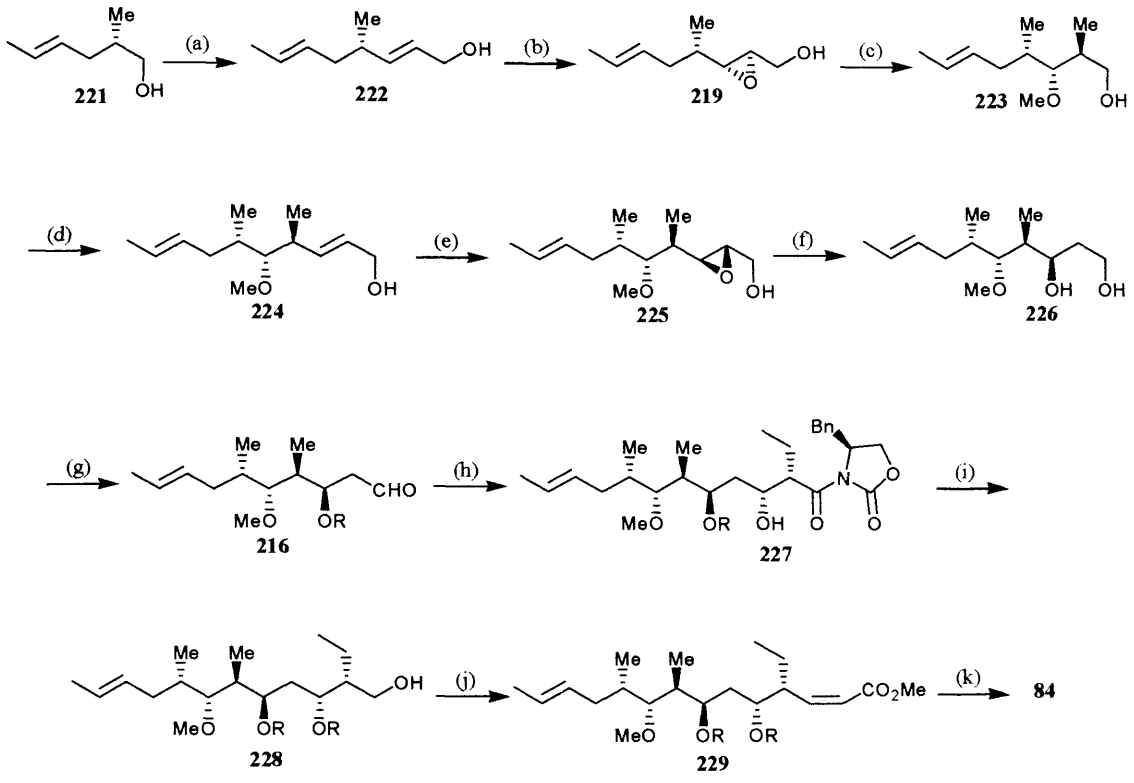
Gurjar and co-workers disclosed two syntheses of **84** (Scheme 4.1),[11] in which the stereochemistry was set *via* combinations of stereoselective epoxide-ring openings and Evans aldol reactions (Scheme 4.2).



Scheme 4.1: Retrosynthetic strategy for pironetin.

The synthesis of **84** was initially attempted using route A in which the Stork-Ueno radical cyclisation was a key step; however, this route was abandoned due to the unsatisfactory yields of some steps. The second route investigated used Sharpless's asymmetric epoxidation reaction and the Evans asymmetric aldol methodology to

establish the stereogenic centres; this resulted in the successful total synthesis of **84** (Scheme 4.2).

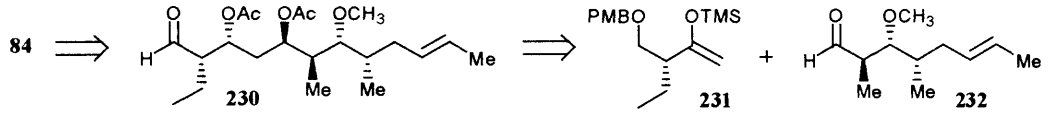


Scheme 4.2. *Reagents and conditions*: (a) (i) IBX, DMSO, 20 °C, 30 min., (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, 20 °C, 3 h, (iii) DIBAL-H, CH_2Cl_2, -20 °C, 30 min.; (b) TBHP, TTIP, (-)-DIPT, CH_2Cl_2, -20 °C, 20 h; (c) (i) Me_2LiCu, Et_2O, -78 °C, 8 h, (ii) TBS-Cl, Im, CH_2Cl_2, 20 °C, 3 h, (iii) KH, MeI, Et_2O, 20 °C, 30 min, (iv) Bu_4NF, THF, 20 °C, 2 h; (d) (i) IBX, DMSO, 20 °C, 30 min., (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, 20 °C, 3 h, (iii) DIBAL-H, CH_2Cl_2, -20 °C, 45 min.; (e) TBHP, TTIP, (+)-DIPT, CH_2Cl_2, -20 °C, 18 h; (f) Red-Al, THF, 0 °C, 4 h; (g) (i) Piv.Cl, Py, CH_2Cl_2, 20 °C, 1 h, (ii) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min., (iii) DIBAL-H, CH_2Cl_2, -20 °C, 20 min., (iv) IBX, DMSO, 20 °C, 30 min.; (h) (*S*)-*N*-butanoyloxazolidinone, Bu_2BOTf, CH_2Cl_2, -78 °C, 6 h; (i) (i) TBS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min., (ii) $LiBH_4$, MeOH-THF, 0-20 °C, 4 h; (j) (i) IBX, DMSO, 20 °C, 30 min., (ii) $(CCl_3CH_2O)_2P{=}CHCO_2Me$, NaH, DMF, -40 °C, 6 h; (k) 1% HCl, EtOH, 20 °C, 12 h.

The stereocentres present in the side-chain of **84** were established mainly from the Sharpless asymmetric epoxidation product, the Evans aldol addition of aldehyde **216**

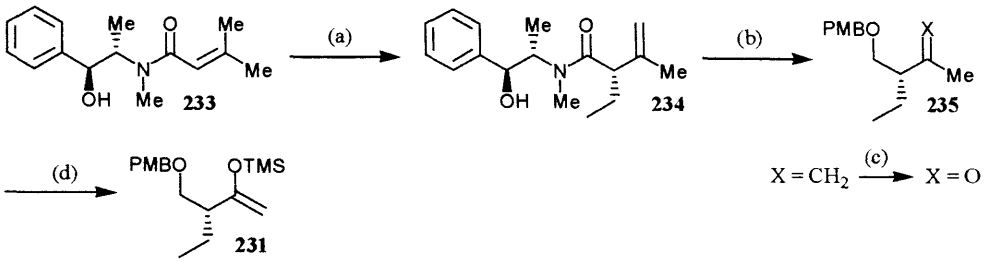
with (*S*)-*N*-butanoyloxazolidinone in the presence of dibutylborontriflate gave **227** with high diastereoselectivity as confirmed by the high resolution ^{1}H NMR spectrum of the aldol product. Oxidation of the terminal alcohol **228** (IBX, DMSO, 20 °C) followed by cis-olifination with modified Horner-Wadsworth-Emmons reaction ($(CCl_3CH_2O)_2POCHCO_2Me$, NaH, DMF, - 40 °C) gave **229** as a sole product. Finally compound **231** was treated with 1% aqueous hydrochloric acid in ethanol at 20 °C for 12 h to give pironetin **84**. Kitahara[14] and Chida[15] have also reported syntheses of **84** in which nucleophilic additions to epoxides play prominent strategic roles.

Scheme 4.3 outlines the synthetic route described by Keck and co-workers towards the synthesis of pironetin **84**, which applies the recently developed lactone annulation procedure to install the lactone moiety by reaction of the lithium enolate of methyl acetate with β-acetoxy aldehyde **230** (Scheme 4.6).[12]

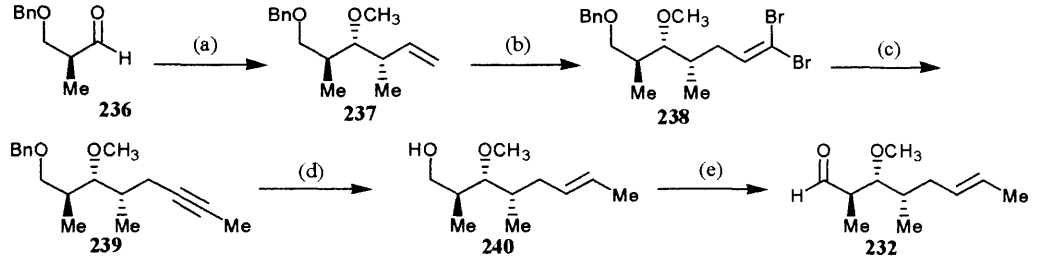


Scheme 4.3: Retrosynthesis of **84**.

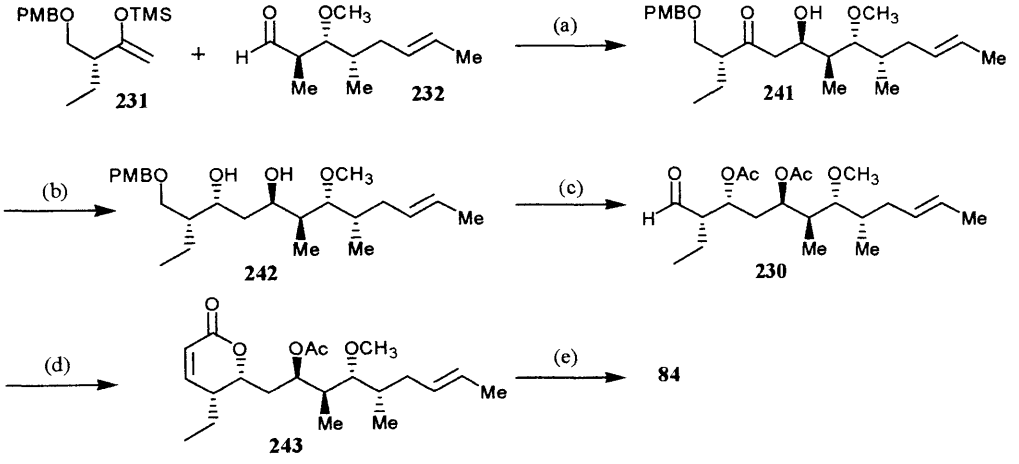
The synthesis of the β-acetoxy aldehyde **230** was achieved by the Lewis acid promoted Mukaiyama aldol reaction of the silyl enol ether **231** and the aldehyde **232**, the preparation of these two intermediates is outlined in Schemes 4.4 and 4.5. The addition reaction of **231** and **232** using $BF_3.Et_2O$ as Lewis acid proceeded to give **241** as a single diastereomer, which underwent samarium diiodide reduction to give the desired diol **242** in good diastereoselectivity (4.6:1). Acylation of the diol, followed by removal of the PMB protecting group, gave the desired primary alcohol, which was oxidised to the corresponding aldehyde **230**. Lactone annulation was effected by the reaction of **230** with the lithium enolate of methyl acetate to give the desired lactone product **241**. Finally, removal of the acetate protecting group by acid-catalysed methanolysis gave (-)-pironetin (Scheme 4.6).



Scheme 4.4: Synthesis of the Enol Ether **231**. *Reagents and conditions*: (a) LDA, LiCl, EtI, 93%; (b) (i) $LiNH_2{:}BH_3$, (ii) KH, PMBBr; (c) OsO_4, $NaIO_5$, 52% from **241**; (d) $(TMS)_2NLi$, TMSCl.

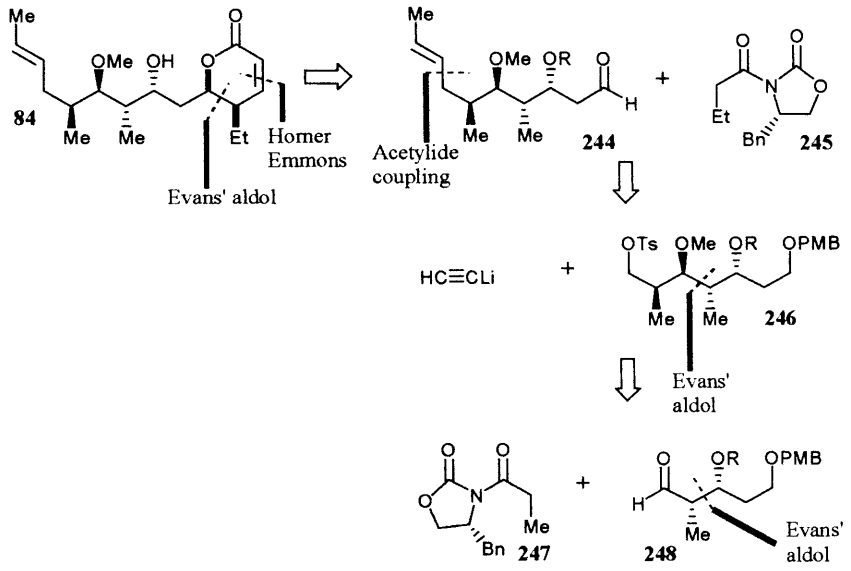


Scheme 4.5: Synthesis of Aldehyde **232**. *Reagents and conditions*: (a) (i) $CH_3CH{=}CHCH_2SnBu_3$, $TiCl_4$, 89%, (ii) KH, MeI, 92%; (b) (i) 9-BBN, H_2O_2, 92%, (ii) TPAP, NMO, (iii) CBr_4, PPh_3, 68% over two steps; (c) BuLi, MeI, 99%; (d) Li/NH_3, 84%; (e) TPAP, NMO.



Scheme 4.6: Total synthesis of pironetin **84**. *Reagents and conditions*: (a) $BF_3.Et_2O$, 86%; (b) SmI_2, THF, MeOH, 91%; (c) (i) DDQ, 92%, (ii) Ac_2O, 97%, (iii) TPAP, NMO; (d) CH=C(OLi)-OMe, 74%; (e) MeOH, 3 N HCl, 65°C, 8 h, 86%.

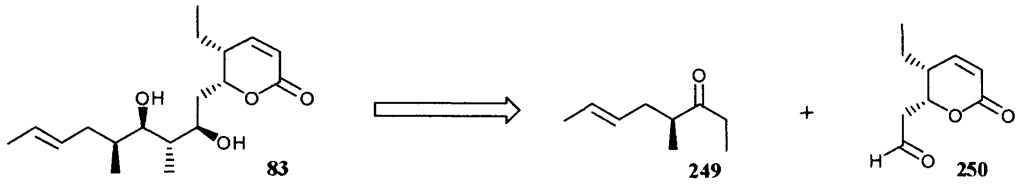
A recent report by Dias and co-workers described the shortest synthetic route to **84** to date, consisting of 18 steps and involving three *syn* aldol reactions to establish the six stereogenic centres (Scheme 4.7). The final steps in this synthesis involved the Horner-Wadsworth-Emmons reaction of the aldehyde **244** using the stabilizing reagent ((*o*-cresol)$_2$P(O)CH$_2$CO$_2$Et) under Ando's conditions to give the corresponding α,β-unsaturated ester (Z:E >95:5).[16] Lactonisation of the α,β-unsaturated ester was achieved by treatment with 1% aqueous hydrochloric acid in ethanol, this furnished the desired product in 11% overall yield from **247**.



Scheme 4.7: Retrosynthetic analysis of pironetin described by Dias and co-workers.

4.3 Results and Discussions

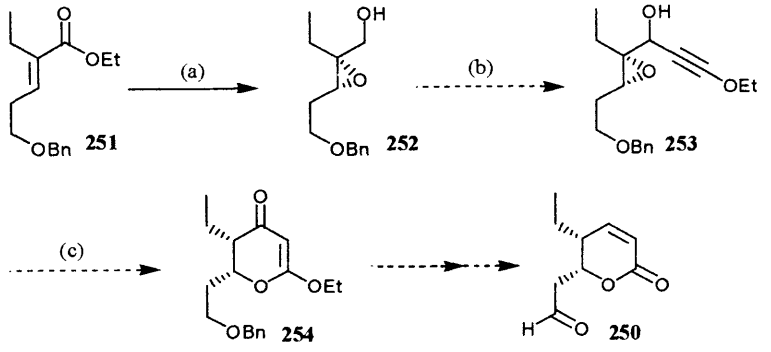
In this chapter the attempted synthesis of NK10958P **83** using chiral boron-mediated cross-aldol coupling of fragments **249** and **250** will be described (Scheme 4.8). As part of this effort two proposed syntheses of the lactonic aldehyde **250** were investigated, the first incorporating a mercury(II) catalysed step to achieve the cyclisation to the dihydropyranone ring (Scheme 4.9). The second method investigated used Keck's annulation procedure,[17] *i.e.* the aldol addition of the lithium enolate of methyl acetate to a β-acetoxy aldehyde intermediate **264** (Scheme 4.22).



Scheme 4.8: Retrosynthetic analysis of NK10958P

4.3.1 Proposed Synthesis of the α,β-Unsaturated Lactone 250 using a Mercury(II)-Catalysed Cyclisation

As outlined in Scheme 4.9, the cyclisation of alkynic epoxy alcohol **253** in the presence of a mercury(II) catalyst was expected to furnish the dihydropyranone **254**, a key intermediate for the synthesis of **250**.

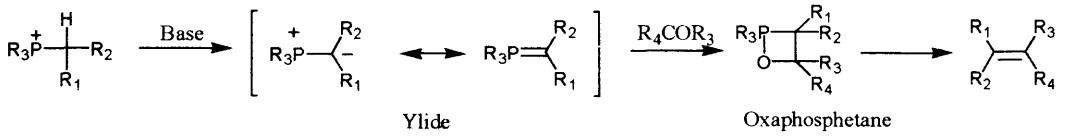


Scheme 4.9: Proposed method for the synthesis of **250**. *Reagents and conditions*: (a) (i) $LiAlH_4$, THF, 20 °C, (ii) TBHP, TTIP, (-)-DET, CH_2Cl_2, -20 °C; (b) (i) SO_3-2Py,

DMSO, NEt_3, 20 °C, (ii) ethoxyacetylene, *n*-BuLi, THF, - 78 °C; (c) HgO, H_2SO_4, acetone, 20 °C.

4.3.1.1 Wittig-Wadsworth-Emmons reaction

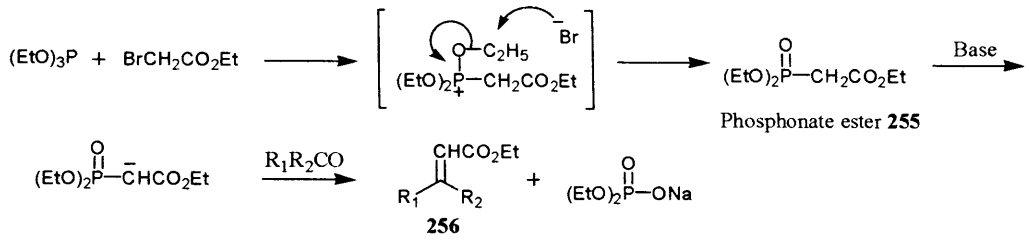
The Wittig-Wadsworth-Emmons reaction is an important reaction in organic synthesis (Scheme 4.10). A strong base (*e.g.* *n*-butyllithium or sodium hydride) is used to generate the ylide that attacks the carbonyl compound. The reaction is believed to occur *via* an oxaphosphetane intermediate and is driven by the strength of the P-O bond that is formed in the phosphine oxide.



Scheme 4.10: Mechanism of the Wittig reaction.

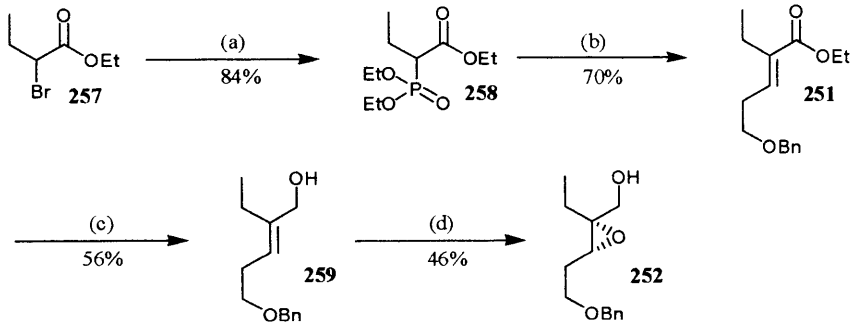
Generally, an unstabilized ylide affords predominantly the *Z*-isomer, while an ylide bearing a stabilising group such as an ester affords mainly or exclusively the *E*-isomer, being more thermodynamically stable on account of steric constraints in the *Z*-isomer.

Phosphonate esters such as **255** also react readily with bases to form ylides (Scheme 4.11). Such ylides will also attack aldehydes and ketones to give α,β-unsaturated acids and esters, a process known as the Wadsworth-Emmons reaction. These phosphonate esters can be prepared by the Arbuzov reaction. One of the advantages of this method is that the phosphate byproduct is water-soluble which simplifies the isolation of the product. Owing to stabilization of the ylide, (*E*)-isomers frequently predominate.

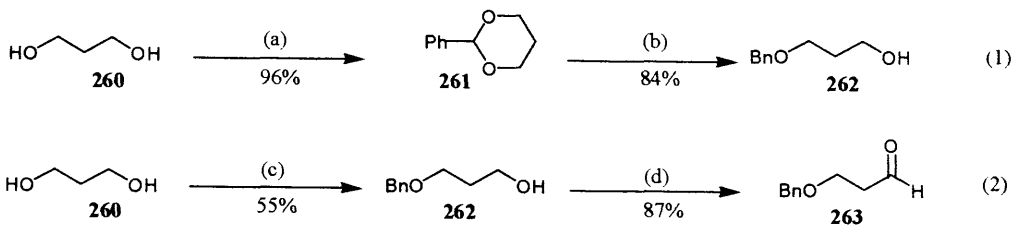


Scheme 4.11: The Arbuzov and Wadsworth-Emmons reactions.

Treating the anion derived from ester phosphonate **258** with the aldehyde **263** under Wadsworth-Emmons conditions afforded **251** (Scheme 4.12); a 1:1 mixture of the E/Z isomers was initially obtained, but the crude product was heated under reflux in diphenyl disulfide for 10 h which resulted in the formation of the (*E*)-isomer **251** as the sole product.[18-20] $LiAlH_4$ reduction in anhydrous ether gave **259**[21] and then Sharpless asymmetric epoxidation gave the epoxide **252**. Scheme 4.13 describes the preparation of aldehyde **263**. However, since the $LiAlH_4$ reduction and epoxidation reactions gave poor yields and also given the large number of steps involved in this proposed route, a shorter route to the α,β-unsaturated lactone **250** was investigated, this is discussed in the next section.



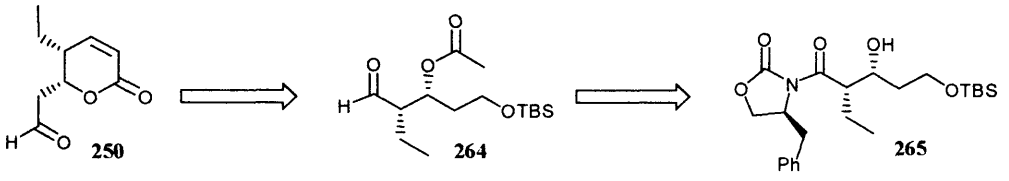
Scheme 4.12. *Reagents and conditions*: (a) $P(OEt)_3$, 160 °C, 5 h; (b) (i) NaH, THF, 0 °C, **263**, 1.5 h, (ii) Ph_2S_2, THF, 65 °C, 10 h; (c) $LiAlH_4$, THF, 20 °C, 20 h; (d) TBHP, TTIP, (-)-DET, CH_2Cl_2, -20 °C, 6 h.



Scheme 4.13: *Reagents and conditions*: (a) PhCHO, *p*-TsOH, toluene, 90 °C, 2.5 h; (b) $AlCl_3$, $LiAlH_4$, ether, 0 °C, 1 h; (c) NaH, BnBr, THF:DMF, 20 °C, 51 h; (d) SO_3-pyridine, NEt_3, DMSO: CH_2Cl_2, 0 °C, 12 h.

4.3.2 Proposed Synthesis of the α,β-Unsaturated Lactone 250 *using Evans Asymmetric Aldol Methodology*

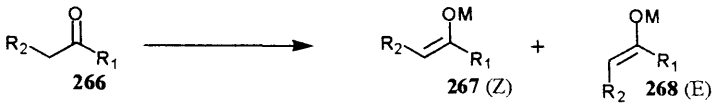
The key step of this route is the Keck annulation procedure, involving the aldol addition of the β-acetoxy aldehyde **264** to the lithium enolate of methyl acetate. The aldehyde **250** could be obtained by the deprotection of the TBS protecting group followed by oxidation (Scheme 4.14).



Scheme 4.14: Proposed synthesis of the lactonic aldehyde fragment of NK10958P using Evans aldol methodology.

4.3.2.1 Evans Asymmetric Aldol Reaction: Introduction

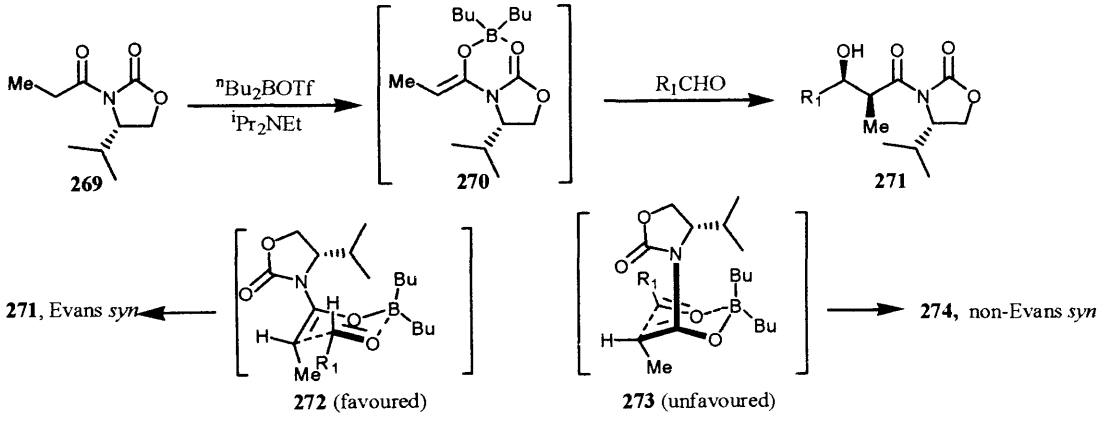
Deprotonation of the keto derivative **266** under kinetic control affords the (*Z*)- and the (*E*)-enolates (Scheme 4.15). Each isomer then reacts with the electrophile (*re*- or *si*-face attack) to give two different enantiomers. In general, the enolate geometry plays an important role in determining the stereochemical outcome of the aldol reaction which proceeds *via* a cyclic transition state. The (*Z*)-enolate reacts with an aldehyde to produce the 1,2-*syn* products, whereas the 1,2-*anti* products arise from the (*E*)-enolate.



Scheme 4.15: Preparation of (*Z*)- and (*E*)-enolates from keto derivatives.

The reaction is believed to occur *via* a six-membered cyclic, Zimmerman-Traxler transition state[22] in which the alkyl group of the aldehyde derivative adopts a pseudo-equatorial position. Furthermore, within 1,2-*syn* or 1,2-*anti* aldol products, enantioselection can be obtained by means of a chiral auxiliary or a chiral ligand-based enolate.

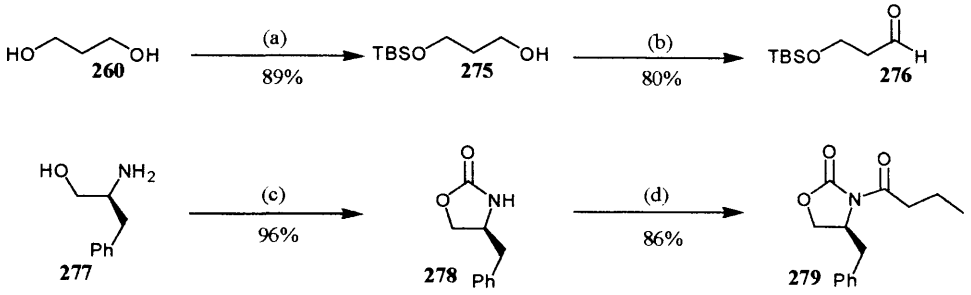
Derived from (*S*)-valine, Evans' 2-oxazolidinone **269** (Scheme 4.16) is an important auxiliary for asymmetric C-C and C-X (X = O, N, Br, F, *etc.*) bond formation. The Evans' aldol reaction involves the application of chiral enolates such as **270** to achieve highly diastereoselective and enantioselective C-C bond formation; high levels of *erythro* diastereoface selection lead to the *syn*-aldol product **271**, the favoured transition state **272** projects the small hydrogen (as opposed to the isopropyl) towards the sterically demanding centre of the transition state. The Evans auxiliary is readily cleaved from the aldol addition product and recycled without any racemization of the aldol product.



Scheme 4.16: The proposed mechanism for the Evans asymmetric aldol reaction.

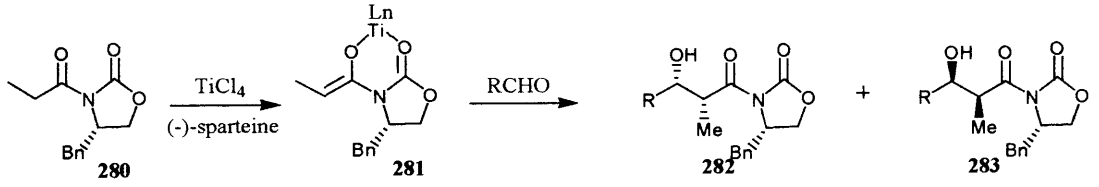
The *N*-butanoyl oxazolidinone **279** was prepared in 85% yield by reacting **278** with butyroyl chloride (1.0 equiv, - 78 °C) (Scheme 4.17).[23] Selective enolisation of **279**

with di-*n*-butylboronyl trifluoromethanesulfonate to form the (*Z*)-enolate, followed by condensation with aldehyde **276** resulted after oxidative work-up in the diastereomeric aldol adduct **265**. However, the aldol addition reaction using this method gave a poor yield (35%) of the aldol **265** along with unreacted *N*-butynyl oxazolidinone **279** (65%).[24,25]



Scheme 4.17: *Reagents and conditions*: (a) TBSCl, imidazole, THF, 20 °C, 14 h; (b) SO_3-pyridine, NEt_3, DMSO, 0 °C, 30 min; (c) K_2CO_3, $CO(OEt)_2$, 135 °C, 2 h; (d) *n*-BuLi, $CH_3(CH_2)_2COCl$, THF, - 78 °C, 1 h.

Scheme 4.18 describes the aldol addition reaction reported by Crimmins and co-workers,[26] where the enolization of 4-benzyl-3-propionyloxazolidin-2-one **280** with titanium tetrachloride (1.1 equiv) and (-)-sparteine (2.5 equiv) followed by the addition of the appropriate aldehyde (1.1 equiv) at 0 °C produced the Evans *syn* adduct, **283** as the major diastereomer in high yield (84-98%) with excellent diastereocontrol (Table 4.1).



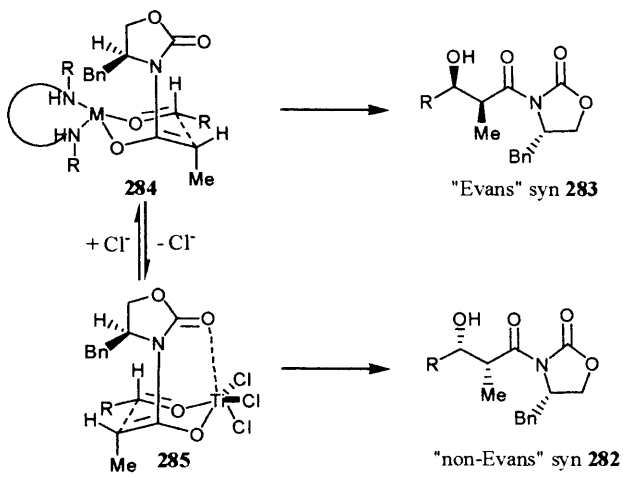
Scheme 4.18: Titanium tetrachloride-mediated aldol addition to **280**.

Table 4.1: Titanium tetrachloride-mediated aldol addition of **280**.

Entry	Temperature	Aldehyde (RCHO)	Yield (%)	**283**:**282**
1	0 °C	Et	84	99:1
2	0 °C	MeCH=CH	89	97:3
3	0 °C	Me_2CH	89	98:2
4	0 °C	*t*-Bu	87	97:3
5	-78 °C	Me_2CH	98	98:2

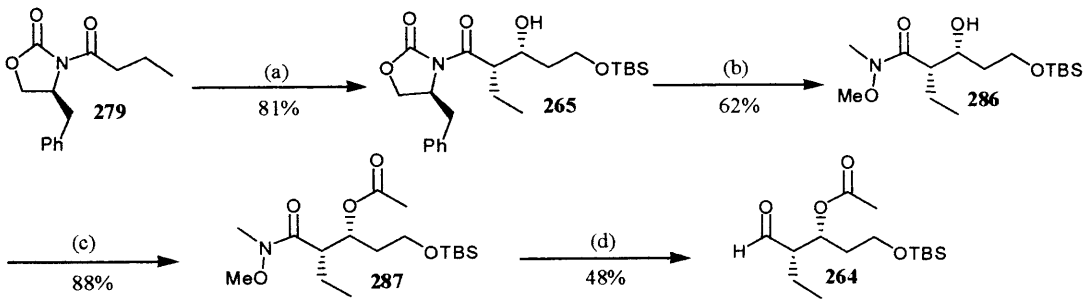
It was observed by Crimmins that the use of 1.05 equiv of titanium tetrachloride, 1.0 equiv of (-)-sparteine, and 1.0 equiv of *N*-methyl-2-pyrrolidinone (NMP) resulted in similar reactivity and diastereocontrol as those observed with 2.5 equiv of (-)-sparteine.[26]

N-Acyloxazolidinones produce Evans *syn* aldol adducts when their chlorotitanium enolates are formed in the presence of 2.0 equiv of (-)-sparteine (or (-)-sparteine/NMP, 1.0 equiv of each). In these instances the non-chelated transition state **284** is operative possibly due to coordination of the second equivalent of the amine to the metal centre, thus preventing coordination of the imide carbonyl to the metal. The same factors that govern the boron enolate transition states would then be operative resulting in the Evans *syn* product. It was observed by the same group that the non-Evans *syn* adducts were obtained simply by the use of 1 equiv of (-)-sparteine and 1 equiv of titanium tetrachloride; this was attributed to the formation of a highly ordered chelated transition state **285** (Scheme 4.19), a model proposed previously by Nagao and Fujita.[27-29]



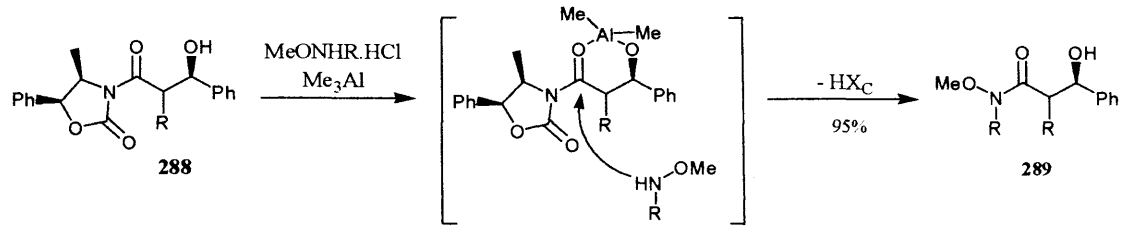
Scheme 4.19: Asymmetric aldol addition using titanium tetrachloride and (-)-sparteine for the enolisation of *N*-acyloxazolidinones.

The above procedure was successfully applied for the synthesis of the aldol product **265** (Scheme 4.20); this procedure was operationally simple as the reagents were used as purchased and no oxidative workup was necessary. The conversion of the chiral imide **265** to an *N*-methoxy-*N*-methylamide, such as **286**, through the use of aluminium amides (prepared *in situ* by the reaction of *N,O*-dimethylhydroxylamine hydrochloride and trimethyl aluminium, CH_2Cl_2, - 15 to 0 °C) was developed by Evans and co-workers.[30,31] The *N*-methoxy-*N*-methylamide is stable and readily converted into its corresponding ketone (using Grignard reagents) or the aldehyde (by DIBAL reduction).[32]



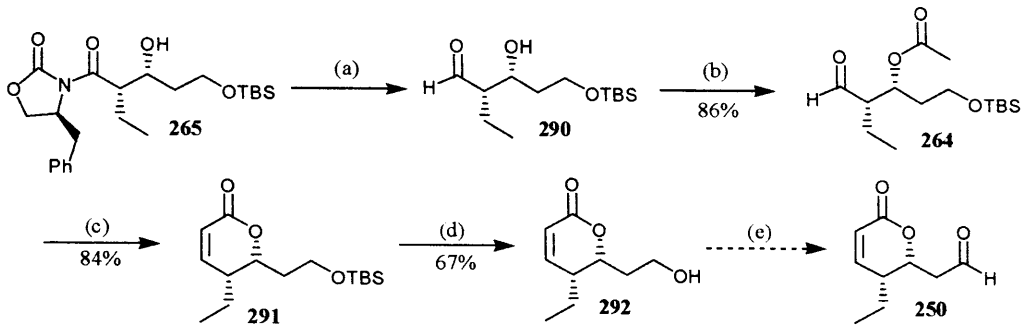
Scheme 4.20: *Reagents and conditions*: (a) $TiCl_4$, (-)-sparteine, **276**, CH_2Cl_2, - 78-20 °C, 2 h; (b) NHMeOMe, $AlMe_3$, CH_2Cl_2, 20 °C, 24 h; (c) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 20 °C, 4 h; (d) DIBAl-H, THF, - 78 °C, 30 min.

The transamidation reaction is favoured by the presence of either an α-heteroatom substituent or a β-alcohol functionality (aldol products). Acceleration of the transamination in the latter case is probably due to the formation of a chelated intermediate (Scheme 4.21), which only activates the exocyclic carbonyl group towards nucleophilic attack.



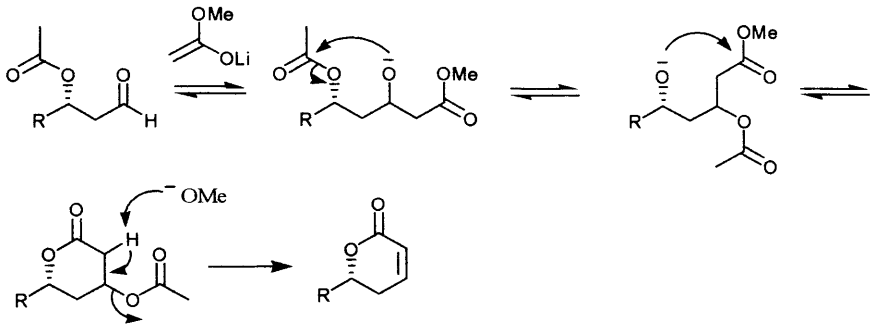
Scheme 4.21: Evans transamination reaction.

Owing to the poor yield of the DIBAL reduction of **287** arising from incomplete conversion, an alternative route to aldehyde **264** was sought, involving Red-Al reduction to cleave the auxiliary and generate the aldehyde functionality, followed by protection of the β-hydroxyl group as the acetate. Owing to the instability of the aldehyde **264**, towards β-elimination and decomposition, the crude material was used directly in the annulation step without further purification. Scheme 4.22 describes the proposed route to the α,β-unsaturated lactone **250**. The protected lactone **291** was synthesized in good yields using Keck's lactone annulation procedure (Scheme 4.23).[17] Removal of the TBS group[33] of lactone **291** was achieved using dilute hydrochloric acid in methanol; however, various attempts at oxidation to aldehyde **250** were unsuccessful,[34,35] the following conditions; SO_3-pyridine, PCC and Swern oxidation gave a crude mixture of products as determined by ^{1}H NMR.



Scheme 4.22: *Reagents and conditions*: (a) Red-Al, THF, - 55 °C, 1 h; (b) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 20 °C, 4 h; (c) LDA, CH_3OAc, THF, - 78 °C, 15 min; (d) HCl (1.0 M), MeOH, 20 °C, 24 h; (e) SO_3-pyridine, NEt_3, DMSO, 0 °C, 30 min.

The Keck annulation reaction is believed to occur by an aldol addition involving the β-acetoxy aldehyde and the lithium enolate of methyl acetate (generated *in situ* by reaction of lithium diisopropyl amide and methyl acetate). Subsequent acyl migration, lactonisation and β-elimination generate the lactone product.

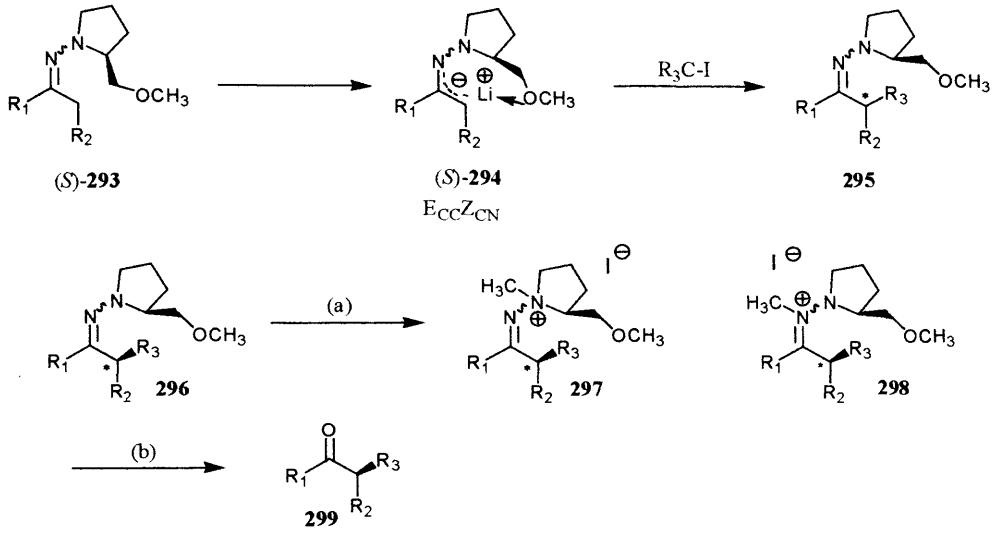


Scheme 4.23: Preparation of α,β-unsaturated lactones.

4.3.3 Synthesis of the Acyclic Ketone Fragment 249

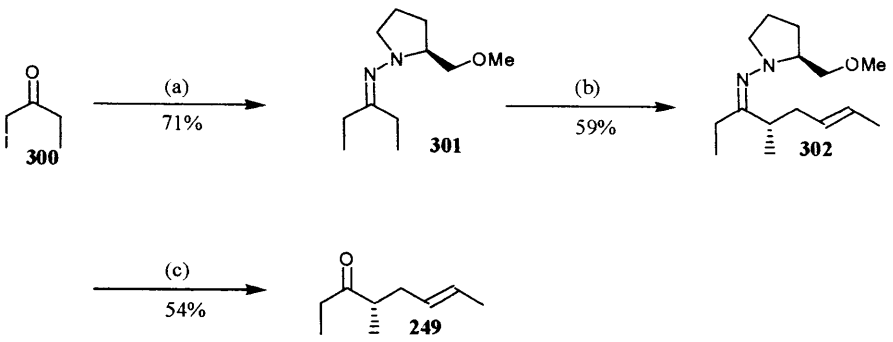
The enantioselective α-propargylation of acyclic ketones was reported by Enders and co-workers to proceed in high enantioselectivity (94-99% ee).[36] Initially, the acyclic ketones were converted into their corresponding "SAMP-hydrazones" (*S*)-**293** by reaction with the enantiomerically pure hydrazine (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP), readily available from (*S*)-proline. Metallation (lithium diisopropylamide in ether at 0 °C) gave the chiral azaenolate (*S*)-**294**, then

alkylation with alkyl iodide furnished the hydrazone **295**. The treatment of **295** with an excess of methyl iodide at 60 °C led to a mixture of the methiodides **297** and **298**. Hydrazone cleavage *via* acidic workup of methiodides **297** in a two-phase system (3-4 N HCl/ *n*-pentane, 60 min) or by ozonolysis led to the α-substituted, enantiomerically enriched acyclic ketones **299** (Scheme 4.24).



Scheme 4.24. *Reagents and conditions*: (a) Excess MeI, 60 °C; (b) 6.0 M HCl, *n*-pentane.

The preparation of the Acyclic Ketone Fragment **249** was achieved using the ((*S*)-1-Amino-2-(methoxymethyl)pyrrolidine) (SAMP) hydrazone **302**, as outlined in Scheme 4.25. Cleavage of the SAMP hydrazone was achieved by the addition of methyl iodide followed by the acid hydrolysis procedure to furnish the enantiopure ketone in 54% yield. The high enantioselectivity was confirmed by the high resolution ^{1}H NMR of the coupled product **302**.



300 301 302 249

Scheme 4.25: *Reagents and conditions*: (a) SAMP, 60 °C, 20 h; (b) (i) LDA, 0 °C, 4 h, (ii) crotyl bromide, 20 °C, 4 h; (c) (i) MeI, 60 °C, 20 h, (ii) HCl (4.0 M), *n*-pentane, 20 °C, 30 min.

4.4 Conclusions

The conversion of the lactonic alcohol **292** into the corresponding aldehyde **250** was a key step in this sequence; use of milder conditions for this reaction, such as Dess-Martin periodate procedure may give the lactonic aldehyde **250**. The crossed-aldol reaction using (-)-diisopinocampheylboron triflate of the aldehyde **250** and ketone **249**,[37] followed by stereoselective reduction of the ketone functionality using tetramethylammonium triacetoxyborohydride ($Me_4NHB(OAc)_3$)[38] is expected to generate the final product NK10958P. This proposed route towards NK10958P could be extended to achieve the synthesis of the methylated derivative pironetin **84**.

Experimental

2-(Diethoxyphosphoryl)butyric acid ethyl ester (258).[39] A mixture of ethyl-2-bromobutyrate (10.0 g, 51.3 mmol) and triethyl phosphite (10.6 g, 64.0 mmol) was heated at 160 °C. After 1 h, a further portion of triethyl phosphite (10.6 g, 64.0 mmol) was added and the heating continued for 4 h. The excess triethyl phosphite was distilled under reduced pressure to give **258** (10.8 g, 84%) as an orange oil which was used in the next step without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (6H, m, CH_2O), 2.78 (1H, dq, J = 10.5, 4.4 Hz, CHP), 1.90 (2H, m, CH_2CH_3), 1.27 (9H, m, CH_3), 0.94 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (C=O), 62.6 (CH_2O), 62.5 (CH_2O), 61.3 (CH_2O), 48.4 (*C*HC), 20.7 (CH_2), 16.3 (CH_3), 14.1 (CH_3), 13.0 (CH_3), 12.8 (CH_3).

5-Benzyloxy-2-ethylpent-2-enoic acid ethyl ester (251).[19] A solution of 2-(diethoxyphosphoryl)butyric acid ethyl ester (2.3 g, 9.15 mmol) in dry tetrahydrofuran (25 mL) was added to a stirred suspension of sodium hydride (0.37 g, 9.15 mmol, 60 % dispersion in oil) in dry tetrahydrofuran (5 mL) at 0 °C. After being stirred at 20 °C for 30 min, a solution of 3-(benzyloxy)propionaldehyde (1.2 g, 7.32 mmol) in dry tetrahydrofuran (25 mmol) was added dropwise at 0 °C and the mixture was stirred for 1 h. The resulting solution was poured onto ice-cooled water (10 mL) and then extracted with ether (3 x 10 mL). The extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and evaporated to give a 1:1 mixture of (*E*)-ester and (*Z*)-ester (1.7 g, 6.5 mmol) as a colourless oil. A solution of the crude product in anhydrous tetrahydrofuran (80 mL) was heated at reflux in the presence of diphenyl disulfide (0.42 g, 1.94 mmol) to give solely the (*E*)-isomer **251** (1.61 g, 70%) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, m, Ph), 6.74 (1H, t, J = 7.0 Hz, *CH*=C), 4.53 (2H, s, O*CH*$_2$Ph), 4.21 (2H, q, J = 7.1 Hz, O*CH*$_2$), 3.56 (2H, t, J = 7.0, *CH*$_2$OBn), 2.50 (2H, q, J = 7.0 Hz, *CH*$_2$CH=), 2.32 (2H, q, J = 7.5 Hz, *CH*$_2$-C=CH), 1.30 (3H, t, J = 7.1 Hz, CH_3), 1.01 (3H, t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C=O), 138.2 (*ipso*-phenyl), 137.7 (phenyl), 135.8 (*C*=CH), 128.4 (C=*CH*), 127.6 (phenyl), 73.0 (O*CH*$_2$Ph), 68.9 (*CH*$_2$OBn), 60.3 (CH_2O), 29.1 (*CH*$_2$CH=C), 20.2 (*CH*$_2$C=CH), 14.3 (*CH*$_3$CH$_2$O), 13.8 (CH_2CH_3).

2-Ethyl-5-phenoxypent-2-en-1-ol (259).[40] A solution of 5-benzyloxy-2-ethylpent-2-enoic acid ethyl ester (1.50 g, 5.65 mmol) in dry tetrahydrofuran (4 mL) was added slowly to a suspension of lithium aluminium hydride (0.10 g, 1.66 mmol) in ether (1.5 mL), at such a rate as to cause gentle reflux. The reaction mixture was stirred at 20 °C; at reaction completion (20 h) the mixture was cooled to 0 °C and quenched by the slow addition of water (3 mL) (CAUTION), then poured into a mixture of 10% aqueous sulfuric acid (3 mL) and crushed ice. The aqueous phase was filtered and extracted with ether (3 x 6 mL) and the solid filtrate was washed with ether (3 x 12 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2 x 60 mL) and brine (2 x 12 mL) and then dried ($MgSO_4$), filtered and evaporated. Column chromatography (10:90 ethyl acetate: petroleum ether) gave **259** (0.70 g, 56%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (5H, m, Ph), 5.41 (1H, t, J = 7.1 Hz, *CH*=C), 4.52 (2H, s, O*CH*$_2$Ph), 4.04 (2H, s, *CH*$_2$OH), 3.49 (2H, t, J = 7.0 Hz, *CH*$_2$OBn), 2.38 (2H, q, J = 7.0, *CH*$_2$CH=C), 2.11 (2H, q, J = 7.6 Hz, *CH*$_2$CH$_3$), 1.00 (3H, t, J = 7.6 Hz, CH$_2$*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2 (*ipso*-phenyl), 142.7 (*C*=CH), 129.3 (*meta*-phenyl), 121.5 (*CH*=C), 120.9 (*para*-phenyl), 119.1 (*ortho*-phenyl), 72.3 (O*CH*$_2$Ph), 70.5 (*CH*$_2$OH), 68.1 (*CH*$_2$OBn), 28.0 (CH_2), 20.3 (CH_2), 11.5 (CH_3).

[2-Ethyl-3-(2-phenoxyethyl)oxiranyl]methanol (252).[40] Crushed 3Å molecular sieves (0.34 g) were added into a flame-dried 50-mL flask cooled under nitrogen. Dichloromethane (17 mL) was added and the flask cooled to – 20 °C. 2-Ethyl-5-phenoxypent-2-en-1-ol (0.65 g, 2.94 mmol), (-)-diethyl tartrate (73 mg, 3.53 mmol), and titanium tetra-isopropoxide (84 mg, 0.29 mmol) were added sequentially, and the mixture was stirred at – 20 °C for 15 min, followed by the slow addition of *tert*-butyl hydroperoxide (1.96 mL, 5.88 mmol, 3.0 M in dichloromethane). After the reaction was complete (6 h) as indicated by TLC, water (2 mL) was added and the mixture stirred for 60 min while allowing it to warm to 20 °C. Hydrolysis of the tartrate was affected by the addition of 30% aqueous sodium hydroxide saturated with sodium chloride and stirring vigorously. The mixture was filtered through a pad of celite and the aqueous layer was extracted with dichloromethane (3 x 50 mL). Evaporation of the volatile solvents gave a residue which was purified by flash column chromatography (20:80 ethyl acetate: hexane), to give **252** (0.30 g, 46%) as a pale

yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (5H, m, Ph), 4.53 (2H, s, O*C*H_2Ph), 3.74 (1H, dd, J = 12.2 and 7.4 Hz, *CH*H*O*H), 3.62 (3H, t, J = 5.7 Hz, O*CH* and CH_2OBn), 3.18 (1H, dd, J = 12.2 and 4.8 Hz, C*H*HOH), 1.96 (1H, m, *CH*HCH_2O), 1.79 (2H, m, *C*$H_2$$CH_3$), 1.50 (1H, m, *CH*H*C*$H_2$O), 1.01 (3H, t, J = 7.0 Hz, CH_2*C*H_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (*ipso*-phenyl), 128.6 (phenyl), 127.7 (phenyl), 73.2 (O*C*H_2Ph), 67.6 (CH_2O), 63.9 (C*CH*O), 63.0 (CH_2OBn), 58.1 (C*CH*O), 28.7 (*C*H_2CHO), 21.8 (*C*H_3), 9.2 (*C*H_2).

2-Phenyl-1,3-dioxane (261).[41] A solution of 1,3-propanediol (3.8 g, 50 mmol) in toluene (13 mL) was treated with benzaldehyde (5.3 g, 50 mmol) and a catalytic amount of *p*-toluenesulfonic acid (15 mg, 7.9 x 10^{-5} mol). The solution was stirred at reflux under a Dean-Stark trap until the theoretical amount of water (~ 0.9 mL) had separated (2.5 h). The mixture was cooled to 20 °C, washed with aqueous sodium hydroxide (2 x 10 mL, 1 M), dried ($MgSO_4$), filtered and evaporated to give **261** (7.9 g, 96%), as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (2H, m, phenyl), 7.34 (3H, m, phenyl), 5.51 (1H, s, *CH*Ph), 4.27 (2H, dd, J = 12.2, 5.0 Hz, CH_2O), 4.00 (2H, t, J = 12.2 Hz, *C*H_2O), 2.23 and 1.47 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (*ipso*-phenyl), 128.8 (phenyl), 127.7 (phenyl), 106.9 (OCH), 65.1 (CH_2O), 33.5 (CH_2).

3-(Benzyloxy)propan-1-ol (262).[42] Anhydrous aluminium chloride (7.3 g, 55 mmol) was added dropwise to dry ether (23 mL) and the solution was cooled to 0 °C with stirring. Lithium aluminium hydride (0.55 g, 14.5 mmol) was slowly added and stirring continued for 30 min, after which a solution of 2-phenyl-1,3-dioxane (4.5 g, 27.5 mmol) in ether (9 mL) was added and the mixture stirred for a further 30 min at 0 °C. 10% aqueous sulfuric acid (45 mL) was added dropwise over 30 min with stirring (CAUTION). The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give **262** (3.85 g, 84%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (5H, m, Ph), 4.73 (2H, s, O*C*H_2Ph), 3.99 (2H, t, J = 5.6 Hz, CH_2O), 3.87 (2H, t, J = 5.6 Hz, CH_2O), 2.17 (1H, bs, *C*O*H*), 2.05 (2H, quintet, J = 5.6 Hz, *C*$H_2$$CH_2$); ^{13}C NMR (75

MHz, $CDCl_3$) δ 138.5 (*ipso*-phenyl), 128.7 (phenyl), 128.1 (phenyl), 127.9 (phenyl), 73.7 (OCH_2Ph), 69.7 (CH_2OBn), 62.3 (CH_2OH), 32.6 (CH_2).

3-(Benzyloxy)propan-1-ol (262).[43] To a solution of sodium hydride (2.5 g, 62.5 mmol, 60 % in oil), in a mixture of tetrahydrofuran (27 mL) and dimethylformamide (17.5 mL) stirred at 0 °C was added dropwise a solution of propane-1,3-diol (4.25 g, 56 mmol) in tetrahydrofuran (13 mL). After stirring at 20 °C for 3 h, benzyl bromide (6.65 mL, 56 mmol) was introduced dropwise. After 48 h the mixture was quenched by the addition of water (30 mL) and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and the organic solvents evaporated. The residue was purified by column chromatography (2:8 ethyl acetate: petroleum ether) to give **262** (4.9 g, 55%) as a colourless oil, with spectroscopic data identical to those given earlier for **262**.

3-(Benzyloxy)propionaldehyde (263).[44] To a solution of alcohol **262** (2.0 g, 12 mmol) in 1:4 dimethyl sulfoxide: dichloromethane (120 mL) at 0 °C was added triethylamine (4.9 g, 48.2 mmol) and SO_3-pyridine (3.83 g, 24.1 mmol) and the resulting solution was stirred at 0 °C for 12 h. The mixture was diluted with ethyl acetate (150 mL) and washed with water (2 x 80 mL), then saturated aqueous ammonium chloride (2x 80 mL) and brine (80 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated, purification by column chromatography gave **263** (1.72 g, 87%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (1H, t, J = 1.8 Hz, *CH*O), 7.32 (5H, s, Ph), 4.57 (2H, s, PhCH_2O), 3.81 (2H, t, J = 6.0 Hz, CH_2O), 2.68 (2H, dt, J = 6.0 and 1.8 Hz, CH_2CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0 (CH=O), 137.9 (*ipso*-phenyl), 128.4 (phenyl), 127.8 (phenyl) 127.7 (phenyl), 73.3 (PhCH_2O), 63.9 (CH_2O), 43.9 (CH_2CHO).

3-(*tert*-Butyldimethylsilanyloxy)-propan-1-ol (275).[44] Imidazole (2.68 g, 39.4 mmol) and *tert*-butyldimethylsilyl chloride (5.94 g, 39.4 mmol) were added consecutively to a stirred solution of the propane-1,3-diol (15.0 g, 0.197 mol) in dry tetrahydrofuran (90 mL) at 0 °C and the resulting cloudy mixture was stirred at 20 °C for 14 h. The mixture was then washed with water (5 x 35 mL) and the organic layer was dried ($MgSO_4$), filtered and evaporated. Purification of the residue by flash

column chromatography (20:80 ethyl acetate: hexane) gave **275** (6.64 g, 89%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.73 (4H, m, CH_2O), 2.58 (1H, bs, OH), 1.70 (2H, m, CH_2), 0.82 (9H, s, $(CH_3)_3CSi$), 0.01 (6H, s, $(CH_3)_2Si$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 62.8 (OCH_2), 62.3 (OCH_2), 34.3 (CH_2), 25.7 ($(CH_3)_3CSi(CH_3)_2$), 18.2 ($(CH_3)_3CSi(CH_3)_2$), -5.5 ($(CH_3)_3CSi(CH_3)_2$).

3-(*tert*-Butyldimethylsilanyloxy)-propionaldehyde (276).[44] To a stirred solution of alcohol **265** (2.50 g, 13.2 mmol) in dimethylsulfoxide (10 mL) at 0 °C was added triethylamine (8.85 g, 87.4 mmol) followed by the slow addition of a solution of SO_3-pyridine (6.30 g, 39.5 mmol) in dimethylsulfoxide (20 mL). The resulting mixture was stirred at 0 °C for 30 min, then added to ice and neutralized with hydrochloric acid (1M). The mixture was extracted with ether (3 x 30 mL) and the combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and evaporated, purification by column chromatography (15:85 ethyl acetate: petroleum ether) gave **276** (2.0 g, 80%) as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.80 (1H, t, J = 2.1 Hz, CHO), 3.98 (2H, t, J = 6.0 Hz, OCH_2), 2.58 (2H, dt, J = 2.1 and 6.0 Hz, CH_2CHO), 0.88 (9H, s, $(CH_3)_3CSi(CH_3)_2$), 0.06 (6H, s, $(CH_3)_3CSi(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 201.9 (CHO), 57.4 (CH_2O), 46.6 (CH_2CO), 25.8 ($(CH_3)_3CSi(CH_3)_2$), 18.2 ($(CH_3)_3CSi(CH_3)_2$), -3.6 ($(CH_3)_3CSi(CH_3)_2$).

2-Amino-3-phenylpropan-1-ol (277).[45] A 1L 3-necked flask was fitted with a magnetic stirrer, a reflux condenser and an addition funnel. The flask was charged with sodium borohydrate (8.20 g, 216 mmol) and anhydrous tetrahydrofuran (240 mL) and L-phenylalanine (15.0 g, 91 mmol). The mixture was cooled to 0 °C and a solution of iodine (22.8 g, 91 mmol) in anhydrous tetrahydrofuran (60 mL) was added dropwise over 30 min. The mixture was heated at reflux for 18 h, it was then cooled to 25 °C and methanol (20 mL) was added slowly, stirring for a further 30 min followed by solvent evaporation gave a white paste. The residue was dissolved in aqueous potassium hydroxide (180 mL, 20%) and stirred for 4 h at 25 °C. The aqueous layer was extracted with dichloromethane (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. Recrystallisation from toluene gave **277** (15.0 g, 92%) as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (5H, m, Ph), 3.63 (1H, dd, J = 10.5 and 3.9 Hz, OC*H*H), 3.38 (1H, dd, J = 10.5 and

7.1 Hz, OCH*H*), 3.13 (1H, m, *CH*NH_2), 2.78 (1H, dd, J = 13.4 and 5.3 Hz, *CH*HPh), 2.54 (1H, dd, J = 13.4 and 8.4 Hz, CH*H*Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 139.2 (*ipso*-phenyl), 128.4 (phenyl), 126.1 (phenyl), 72.2 (*CH_2*OH), 57.0 (*CH*NH_2), 39.5 (*CH_2*Ph).

(*4S*)-4-(Phenylmethyl)-2-oxazolidinone (278).[46] A dry 500 mL 3-necked round-bottomed flask equipped with a thermometer and an 18-in Vigreux column with a distillation head was charged with alcohol **277** (2.0 g, 13.2 mmol), potassium carbonate (0.18 g, 1.32 mmol) and diethyl carbonate (3.2 g, 26.8 mmol). The mixture was carefully heated to 135-140 °C, and ethanol was allowed to distil as it was formed. After 2 h, the light brown slurry was cooled to 20 °C, diluted with dichloromethane (10 mL) and filtered to remove most of the remaining potassium carbonate. The mixture was washed with aqueous sodium hydrogen carbonate (2 x 10 mL, 1 M). The organic layer was dried ($MgSO_4$), filtered and evaporated to give a pale yellow crystalline solid. Recrystallization (ethyl acetate/ petroleum ether) gave **278** (2.24 g, 96%) as a colourless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.33 (3H, m, phenyl), 7.19 (2H, m, phenyl), 4.97 (1H, bs, NH), 4.49 (1H, t, J = 6.1 Hz, *CH*HO), 4.16 (1H, t, J = 6.1 Hz, CH*H*O), 4.10 (1H, m, *CH*N), 2.88 (2H, m, *CH_2*Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.2 (C=O), 136.0 (*ipso*-phenyl), 129.0 (phenyl), 127.3 (phenyl), 69.6 (CH_2O), 53.8 (*CH*N), 41.5 (*CH_2*Ph).

4-Benzyl-3-butyryloxazolidin-2-one (279).[47] To a stirred solution of (*4S*)-4-(phenylmethyl)-2-oxazolidinone (1.0 g, 5.65 mmol) in dry tetrahydrofuran (28 mL) at – 78 °C under an atmosphere of nitrogen, was added *n*-butyllithium (2.5 mL, 5.65 mmol, 1.6 M solution in hexanes), after stirring for 15 min, the solution was treated with butyryl chloride (0.60 g, 5.65 mmol) and then stirred for a further 1 h at – 78 °C. The mixture was warmed up to 20 °C, then poured into a mixture of ethyl acetate (27 mL) and saturated aqueous ammonium chloride (11 mL). The separated organic layer was washed successively with saturated aqueous ammonium chloride (11 mL), saturated aqueous sodium hydrogen carbonate (27 mL) and brine (27 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give **279** (1.2 g, 86%) as a brown oil; IR ν_{max} (cm^{-1}) 1782 (C=O), 1700 (NC=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.29 (3H, m, phenyl), 7.22 (2H, m, phenyl), 4.67 (1H, m, CHN), 4.15 (2H, m,

OCH_2), 3.29 (1H, dd, J = 10.2 and 2.4 Hz, *CH*HPh), 2.92 (2H, m, CH_2C=O), 2.76 (1H, dd, J = 10.2 and 7.2 Hz, CH*H*Ph), 1.73 (2H, sextet, J = 5.7 Hz, CH_2), 1.01 (3H, t, J = 5.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.2 (C=O), 153.5 (NC=O), 135.3 (*ipso*-phenyl), 129.4 (phenyl), 129.0 (phenyl), 127.3 (phenyl), 66.2 (CH_2O), 55.1 (CH_2N), 37.9 (CH_2Ph), 37.4 (CH_2), 17.7 (CH_2), 13.7 (CH_3); LRMS m/z (%)+CI 248 (M^+, 50 %), 206 (20), 179 (10), 178 (100), 156 (5); HRMS calcd for $C_{14}H_{17}O_3N$ 248.12812 (M+H), found 248.12885.

4-Benzyl-3-[5-(*tert*-butyldimethylsilanyloxy)-2-ethyl-3-hydroxypentanoyl]-oxazolidin-2-one (265). To a solution of 4-benzyl-3-butyryloxazolidin-2-one (3.50 g, 14.1 mmol) in anhydrous dichloromethane (120 mL) at 0 °C was added titanium tetrachloride (14.8 mL, 14.8 mmol, 1.0 M in dichloromethane). After stirring for 5 min (-)-sparteine (3.31 g, 14.1 mmol) was added dropwise and the mixture was stirred at 0 °C for 20 min, it was then cooled to -78 °C, and 1-methyl-2-pyrrolidinone (1.40 g, 14.1 mmol) was added. After stirring for 10 min 3-(*tert*-butyldimethylsilanyloxy)-propionaldehyde (2.9 g, 15.3 mmol) was added dropwise. The mixture was stirred for 1 h at -78 °C, then gradually warmed to 0 °C, and stirred for 1 h. The reaction was warmed to 20 °C and quenched with half-saturated aqueous ammonium chloride (17.5 mL). The aqueous layer was extracted with dichloromethane (2 x 15 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvents evaporated. Purification by column chromatography (20:80 ethyl acetate: petroleum ether) gave **265** (5.0g, 81%) as a pale yellow oil; $[\alpha]_D$ = + 50.3 (c 1.28, $CHCl_3$); IR ν_{max} (cm^{-1}) 3469 (OH), 1780 (C=O), 1692 (NC=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.30 (3H, m, phenyl), 7.23 (2H, m, phenyl), 4.71 (1H, m, CHN), 4.12 (3H, m, CH_2O, CHOH), 3.85 (2H, m, CH_2OTBS), 3.34 (1H, dd, J = 13.3 and 3.1 Hz, *CH*HPh), 2.71 (1H, dd, J = 13.3, 10.1 Hz, CH*H*Ph), 1.71 (5H, m, *CH*C=O, $2CH_2$), 0.98 (3H, t, J = 7.5 Hz, CH_3), 0.88 (9H, s, $(CH_3)_3$CSi$(CH_3)_2$), 0.06 (6H, s, $(CH_3)_3$CSi$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 175.2 (C=O), 153.4 (NC=O), 135.4 (*ipso*-phenyl), 129.4 (phenyl), 128.9 (phenyl), 127.3 (phenyl), 71.9 (CHOH), 65.9 (CH_2O), 62.3 (CH_2O), 55.6 (CHN), 49.5 (*CH*C=O), 38.1 (CH_2Ph), 35.8 (CH_2COH), 25.9 $(CH_3)_3$CSi$(CH_3)_2$), 20.9 (CH_2), 18.2 $(CH_3)_3$*C*Si$(CH_3)_2$), 11.6 (CH_3); LRMS m/z (%)+CI 436 (M^+, 85 %), 418 (75), 388

(100), 330 (40), 304 (55), 259 (40), 248 (60), 218 (25), 206 (70); HRMS calcd for $C_{23}H_{37}O_5NSi$ 436.2514 (M+H), found: 436.2520.

5-(*tert*-Butyldimethylsilanyloxy)-2-ethyl-3-hydroxypentanoic acid *N*-methoxy-*N*-methyl-amide (286). To a suspension of *N,O*-dimethylhydroxylamine hydrochloride (0.50 g, 5.06 mmol) in anhydrous dichloromethane (10 mL) at 0 °C was added trimethylaluminium (2.5 mL, 5.06 mmol, 2.0 M in toluene) over 5 min (CAUTION: vigorous gas evolution). The solution was warmed to 20 °C and stirred for 30 min; it was then cooled to - 15°C and a solution of 4-benzyl-3-[5-(*tert*-butyldimethylsilanyloxy)-2-ethyl-3-hydroxypentanoyl]-oxazolidin-2-one (1.10 g, 2.53 mol) in dichloromethane (7.0 mL) was added. After stirring at 0 °C for 30 min, the mixture was cooled to – 10 °C and allowed to warm to 20 °C overnight. An aqueous solution of tartaric acid (13.5 mL, 1 M) was added *via* a cannula and the resulting mixture was vigorously stirred for 1 h. The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and evaporated. Purification by flash column chromatography (30:70 ethyl acetate: petroleum ether) gave **286** (0.51 g, 62%) as an orange oil; $[\alpha]_D = +5.7$ (c 1.03, $CHCl_3$); IR ν_{max} (cm^{-1}) 3342 (OH), 1755 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ_H 3.83 (3H, m, CH_2O and CHOH), 3.77 (3H, s, OCH_3), 3.17 (3H, s, NCH_3), 1.71 (2H, m, CH_2CH), 1.61 (1H, m, $CHCH_2$), 1.30 (2H, m, CH_2), 0.87 (12 H, s, $(CH_3)_3CSi(CH_3)_2$ and CH_3), 0.04 (6H, s, $(CH_3)_3CSi(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.5 (C=O), 72.4 (CHOH), 62.4 (CH_2O), 61.4 (OCH_3), 47.6 (NCH_3), 36.3 (CH_2CHOH), 25.8 ($(CH_3)_3CSi(CH_3)_2$), 20.9 (CH_2), 18.1 ($(CH_3)_3CSi(CH_3)_2$), 12.0 (CH_3); LRMS m/z (%)+CI 320 (M^+, 45 %), 304 (20), 259 (30), 188 (30), 178 (100), 117 (15), 102 (50), 89 (30); HRMS calcd for $C_{15}H_{33}O_4NSi$ 320.2252 (M+H), found 320.2255.

Acetic acid 1-[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-2-(*N*-methoxy-*N*-methyl-carbamoyl)-butyl ester (287). To a stirred solution of 5-(*tert*-butyldimethylsilanyloxy)-2-ethyl-3-hydroxypentanoic acid *N*-methoxy-*N*-methyl-amide (0.15 g, 0.47 mmol), in dichloromethane (1.2 mL) at 20 °C was added acetic anhydride (72 mg, 0.70 mmol), triethylamine (80 mg, 0.72 mmol) and a catalytic amount of DMAP (0.57 mg). The mixture was stirred for 4 h and then diluted with

ether (7.5 mL), the mixture was then washed with brine (2 x 5 mL) and the organic layer was dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography (15:85 ethyl acetate: petroleum ether) gave **287** (0.15 g, 88%) as a yellow oil; $[\alpha]_D = +46.2$ (c 0.87, $CHCl_3$); IR ν_{max} (cm^{-1}) 1748 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ_H 3.63 (3H, s, OCH_3), 3.57 (2H, m, CH_2O), 3.45 (1H, q, J = 5.3 Hz, O*CH*), 3.17 (3H, s, NCH_3), 2.02 (3H, s, $CH_3C=O$), 1.82 (4H, m, CH_2), 1.48 (1H, m, *CH*CH_2), 0.86 (12 H, s, *(CH₃)₃*CSi$(CH_3)_2$, and CH_3), 0.04 (6H, s, $(CH_3)_3CSi$*(CH₃)₂*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.6 (C=O), 166.4 (CH_3C=O), 65.8 (O*CH*), 61.4 (CH_3O), 59.4 (CH_2O), 45.2 (CH_3N), 33.9 (CH_2), 25.9 *(CH₃)₃*CSi$(CH_3)_2$), 22.1 (CH), 21.3 (CH_2), 21.1 (CH_3C=O), 18.2 $(CH_3)_3$*C*Si$(CH_3)_2$), 12.1 (CH_3); LRMS m/z (%)+CI 362 (M^+, 35 %), 346 (15), 304 (15), 302 (20), 242 (20), 241 (30), 230 (35), 178 (100), 170 (15); HRMS calcd for $C_{17}H_{35}O_5NSi$ 362.2357 (M+H), found 362.2364.

Acetic acid 1-[2-(tert-butyldimethylsilanyloxy)-ethyl]-2-formylbutyl ester (264). To a solution of acetic acid 1-[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-2-(*N*-methoxy-*N*-methyl-carbamoyl)-butyl ester (0.50 g, 1.38 mmol) in anhydrous tetrahydrofuran (12 mL) at – 78 °C was added DIBALH (1.4 mL, 1.38 mmol, 1.0 M solution in toluene). After stirring for 30 min, the solution was added to a 1:1 mixture of diethyl ether: 1M aqueous hydrochloric acid (20 mL). This mixture was allowed to warm to 20 °C, and the separated organic layer was washed with brine (15 mL) and dried ($MgSO_4$). Filtration and evaporation gave **264** (0.2 g, 48%) as a colourless oil that was used without further purifications.

5-(*tert*-Butyldimethylsilanyloxy)-2-ethyl-3-hydroxypentanal (290). To a 100 mL flame-dried flask charged with anhydrous tetrahydrofuran (15 mL) was added sodium *bis*(2-methoxyethoxy) aluminium hydride (Red-Al) (0.40 mL, 1.27 mmol). The mixture was cooled to – 78 °C and a solution of the ester **265** (0.50 g, 1.15 mmol) in tetrahydrofuran (10 mL) was added slowly. After 15 min the solution was warmed to – 55 °C and stirred for 1 h. The reaction was quenched at that temperature by the addition of ethyl acetate (1.9 mL) followed by methanol (0.5 mL). The mixture was poured into a solution of hydrochloric acid (6.6 mL, 1.4 mL) and ether (14 mL) at -20 °C, stirred for 15 min and the organic layer decanted from the frozen aqueous layer. The organic layers were dried (K_2CO_3), filtered and

evaporated to give **290** (0.42 g), that was used immediately without further purification.

Acetic acid 1-[2-(tert-butyldimethylsilanyloxy)-ethyl]-2-formylbutyl ester (264). To a solution of 5-(*tert*-butyldimethylsilanyloxy)-2-ethyl-3-hydroxypentanal (0.40 g, 1.54 mmol) in dichloromethane (5 mL) at 20 °C was added acetic anhydride (0.23 g, 2.31 mmol), triethylamine (0.25 g, 2.46 mmol) and a catalytic amount of DMAP (19 mg). The mixture was stirred for 4 h, then diluted with ether (15 mL), washed with brine (12 mL) and the organic layers were dried ($MgSO_4$), filtered and evaporated to give **264** (0.30 g, 86%) that was used without further purification.

6-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-5-ethyl-5,6-dihydropyran-2-one (291). To a stirred solution of diisopropylamine (0.19 g, 1.89 mmol) in anhydrous tetrahydrofuran (20 mL) at 0 °C was added *n*-butyllithium (0.69 mL, 1.72 mmol, 2.5 M in hexanes). After 20 min at 0 °C the solution was cooled to – 78 °C; methyl acetate (0.14 g, 1.89 mmol) was added and stirring was continued for 15 min. A solution of acetic acid 1-[2-(tert-butyldimethylsilanyloxy)-ethyl]-2-formylbutyl ester (0.52 g, 1.72 mmol) in anhydrous tetrahydrofuran (7 mL) cooled to – 78 °C was transferred into the enolate solution via cannula. Stirring was continued for 15 min at which time TLC analysis indicated the absence of the aldehyde **264**. The mixture was warmed to 0 °C, stirred for an additional 30 min and finally warmed to 20 °C for 15 min. The solution was transferred via cannula into an Erlenmeyer flask containing a pH 7 buffer (83 mL) and dichloromethane (83 mL). The organic layer was separated, kept and the aqueous layer was extracted with dichloromethane (2 x 35 mL) followed by ethyl acetate (1 x 35 mL). The combined organic layers were dried ($MgSO_4$), filtered through a pad of celite and evaporated. The residue was purified by flash column chromatography (10:90 ethyl acetate: petroleum ether) to give **291** (0.18 g, 84%) as a colourless oil; $[\alpha]_D = +67.8$ (c 1.12, $CHCl_3$); IR ν_{max} (cm^{-1}) 1728 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.98 (1H, dd, J = 9.8, 3.8 Hz, *CH*=CHC=O), 6.01 (1H, d, J = 9.8 Hz, CH=*CH*C=O), 4.62 (1H, dt, J = 9.4 and 3.8 Hz, OCH), 3.75 (2H, m, CH_2O), 2.26 (1H, m, CH), 1.93-1.64 (4H, m, $2CH_2$), 0.93 (3H, t, J = 7.5, CH_3), 0.85 (9H, s, $(CH_3)_3CSi(CH_3)_2$), 0.03 (6H, s, $(CH_3)_3CSi(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.4 (C=O), 150.5 (*CH*=CHC=O), 120.8

(CH=*CH*C=O), 76.6 (OCH), 58.8 (CH_2O), 38.5 (*CH*), 34.2 (CH_2), 25.9 ($(CH_3)_3CSi(CH_3)_2$), 20.8 (CH_2), 18.2 ($(CH_3)_3CSi(CH_3)_2$), 10.9 (CH_3), -5.4 ($(CH_3)_3CSi(CH_3)_2$); LRMS m/z (%)+CI 285 (M^+, 100 %), 269 (80), 227 (95), 209 (25), 181 (20), 153 (95), 135 (60), 107 (50), 81 (20); HRMS calcd for $C_{15}H_{28}O_3Si$ 285.1886 (M+H), found 285.1883.

5-Ethyl-6-(2-hydroxyethyl)-5,6-dihydropyran-2-one (292). To a stirred solution of 6-[2-(*tert*-butyldimethylsilanyloxy)-ethyl]-5-ethyl-5,6-dihydropyran-2-one (0.20 g, 0.70 mmol) in methanol (17 mL) at 20 °C was added hydrochloric acid (2.8 mL, 1.0 M). After stirring for 22 h, the methanol was evaporated and the remaining aqueous residue was extracted with ether (3 x 10 mL). The combined organic layers were washed with 5% aqueous sodium carbonate (2 x 10 mL) followed by brine (10 mL), and then dried ($MgSO_4$), filtered and evaporated. Flash column chromatography (1:1 ethyl acetate: petroleum ether) gave **292** (80 mg, 67%) as a pale yellow oil; $[\alpha]_D$ = + 52.0 (c 0.79, $CHCl_3$); IR ν_{max} (cm^{-1}) 3372 (OH), 1731 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.99 (1H, dd, *J* = 9.8, 5.9 Hz, *CH*=CHC=O), 5.97 (1H, d, *J* = 9.8 Hz, CH=*CH*C=O), 4.67 (1H, dt, *J* = 10.1 and 3.6 Hz, OCH), 3.81 (2H, m, CH_2O), 2.57 (1H, bs, OH), 2.28 (1H, m, CH), 2.00-1.47 (4H, m, CH_2), 0.94 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.8 (C=O), 151.0 (*CH*=CHC=O), 120.5 (CH=*CH*C=O), 77.8 (OCH), 58.5 (CH_2O), 38.5 (CH), 33.8 (CH_2), 20.7 (CH_2), 10.9 (CH_3); LRMS m/z (%)+CI 170 (15), 169 (M^+, 100 %), 166 (25), 27 (5); HRMS calcd for $C_9H_{14}O_3$ 169.0870 (M+H), found 169.0875.

Attempted Synthesis of (3-Ethyl-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)-acetaldehyde (250). To a solution of 5-ethyl-6-(2-hydroxyethyl)-5,6-dihydropyran-2-one (0.20 g, 1.18 mmol) in dimethylsulfoxide (1.0 mL) at 0 °C was added triethylamine (0.78 g, 7.8 mmol) and a solution of SO_3-pyridine (0.56 g, 3.53 mmol) in dimethylsulfoxide (2.0 mL). The resulting solution was stirred at 0 °C for 30 min, poured onto ice and then neutralized with dilute hydrochloric acid. The aqueous solution was extracted with ether (3 x 15 mL) and the combined organic layers were washed with brine (2 x 10 mL), dried ($MgSO_4$) filtered and evaporated to give pale yellow oil that was shown by NMR to be a mixture of products.

(1-Ethylpropylidene)-((*S*)-2-methoxymethylpyrrolidin-1-yl)-amine (301).[36] A solution of SAMP (0.50 g, 3.84 mmol) and 3-pentanone (0.34 g, 3.92 mmol) was heated under reflux (bath temperature at 60 °C) for 20 h. When the reaction was complete (determined by TLC and IR), the mixture was cooled to 20 °C and poured into dichloromethane and water (6:1, 21 mL). The separated organic layer was dried ($MgSO_4$), filtered and evaporated to give **301** (0.60 g, 71%) suitable for prompt conversion into **302**; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.39-3.20 (4H, m, OCH_2, NCH_2), 3.32 (3H, s, OCH_3), 2.40-1.80 (9H, m, $2CH_2$ of ring, $2CH_2$ of chain, NCH), 1.05 (6H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.7 (C=N), 75.4 (CH_2O), 66.0 (CHN), 59.1 (CH_3O), 55.0 (CH_2N), 28.7 (CH_2), 26.6 (CH_2), 23.4 (CH_2), 21.9 (CH_2), 11.9 (CH_3), 11.0 (CH_3).

(*E*)-1-Bromobut-2-ene.[48] A solution of the but-2-en-1-ol (3.0 g, 42 mmol) in anhydrous ether (15 mL) was cooled to 0 °C and treated dropwise with freshly distilled phosphorus tribromide (2.0 mL, 7.4 mmol). The mixture was stirred for 3 h at 10 °C before being poured onto ice (45 g). The separated organic layer was washed successively with water (20 mL), saturated aqueous potassium carbonate (20 mL) and brine (20 ml). Then the organic layer was dried ($MgSO_4$), filtered and evaporated at atmospheric pressure to give (*E*)-1-bromobut-2-ene (4.0 g, 70%) as a colourless liquid, which was used immediately and without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.74 (2H, m, *CH=CH*), 3.93 (2H, d, J = 6.5 Hz, CH_2Br), 1.73 (3H, d, J = 6.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 131.4 (CH_3CH=CH), 127.5 (CH_3CH=*CH*), 33.6 (*CH*$_2$Br), 17.7 (CH_3).

[(*E*)-(*S*)-1-Ethyl-2-methylhex-4-en-(*Z*)-ylidene]-((*S*)-2-methoxymethylpyrrolidin-1-yl)-amine (302). *n*-Butyllithium (0.64 mL, 1.60 mmol, 2.5 M solution in hexanes) was added dropwise to a solution of diisopropylamine (0.16 g, 1.60 mmol) in anhydrous ether (5 mL) at 0 °C. After 15 min (1-ethylpropylidene)-((*S*)-2-methoxymethylpyrrolidin-1-yl)-amine (0.30 g, 1.50 mmol) was added and the mixture was stirred at 0 °C for 4 h. The mixture was then cooled to - 110 °C and a solution of crotyl bromide (0.21 g, 1.6 mmol) in anhydrous ether (2 mL) was added. Stirring was continued at - 110 °C for 1 h and then allowed to warm to 20 °C over 4 h. The mixture was poured into water and ether (1:2, 30 mL) and the separated

organic layer was washed with water (2 x 15 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated, the residue oil was purified by column chromatography (50:50 diethyl ether: petroleum ether) to give **302** (0.20 g, 59%) as a pale yellow oil; $[\alpha]_D = +16.5$ (c 0.61, $CHCl_3$); IR ν_{max} (cm^{-1}) 1607 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.41 (1H, m, CH_3CH=CH), 5.28 (1H, m, CH_3CH=CH), 3.57 (1H, m, NCH), 3.32 (4H, m, OCH_3, NCHH), 3.16 (2H, q, J = 8.0 Hz, OCH_2), 2.96 (1H, m, NCHH), 2.42-1.81 (8H, m, β-ring $2CH_2$, N=CCH_2, CH_2), 1.64 (4H, m, CH, C=CCH_3), 1.09 (3H, t, J = 7.4, CH_3), 1.02 (3H, d, J = 7.1, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.0 (C=N), 129.1 (CH_3CH=CH), 126.0 (CH_3CH=CH), 76.0 (OCH_2), 65.9 (OCH_3), 59.2 (CHN), 55.2 (NCH_2), 37.4 (CHC=N), 34.7 (CH_2), 26.8 (CH_2), 23.9 (CH_2), 21.9 (CH_2), 17.9 (CH_3), 17.7 (CH_3), 12.3 (CH_3); LRMS m/z (%)+CI 253 (M^+, 70 %), 242 (55), 210 (42), 195 (25), 151 (30), 129 (20), 116 (45), 114 (22), 70 (15); HRMS calcd for $C_{15}H_{28}ON_2$ 253.2274 (M+H), found 253.2278.

(*E*)-(*S*)-4-Methyloct-6-en-3-one (249). SAMP hydrazone **302** (0.20 g, 0.79 mmol) was dissolved in methyl iodide (0.56 g, 3.97 mmol) and the solution was heated under reflux for 20 h. The excess methyl iodide was then removed *in vacuo* and the remaining viscous brown oil was dissolved is aqueous hydrochloric acid (5 mL, 4 M) and stirred for 5 min at 20 °C, *n*-pentane (20 mL) was then added and the mixture was stirred vigorously for 30 min. The organic layer was separated and washed with aqueous sodium hydrogen sulfite (3 mL) followed by pH 7 buffer solution (3 mL), and then dried over $MgSO_4$. The solvents were filtered and evaporated and the remaining oil was purified by kugelrohr distillation to give **249** (60 mg, 54%) as a colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.44 (1H, m, CH_3CH=CH), 5.28 (1H, m, CH_3CH=CH), 2.56 (1H, sextet, J = 6.9 Hz, $CH$$CH_3$), 2.41 (2H, q, J = 7.1 Hz, CH_2C=O), 2.26 (1H, m, CH_2C=C), 2.03 (1H, m, CH_2C=C), 1.63 (3H, d, J = 6.9 Hz, CHCH_3), 1.03 (6H, m, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 215.0 (C=O), 128.1 (CH_3CH=CH), 127.3 (CH_3CH=CH), 46.2 (CH), 36.1 (CH_2), 34.5 (CH_2), 17.9 (CH_3), 16.1 (CH_3), 7.7 (CH_3). Spectroscopic data were identical to those reported in the literature.[49]

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Table 1. Crystal data and structure refinement.

Identification code	**05src0001 (EE1/UCL)**	
Empirical formula	$C_{14}H_{16}O_3$	
Formula weight	232.27	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.2521(3) Å	α = 90°
	b = 9.3237(17) Å	β = 90°
	c = 20.809(4) Å	γ = 90°
Volume	1213.0(3) Å^3	
Z	4	
Density (calculated)	1.272 Mg / m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	496	
Crystal	Slab; colourless	
Crystal size	0.34 × 0.15 × 0.12 mm^3	
θ range for data collection	2.93 – 27.48°	
Index ranges	$-8 \le h \le 7$, $-11 \le k \le 12$, $-27 \le l \le 24$	
Reflections collected	27007	
Independent reflections	2773 [R_{int} = 0.0356]	
Completeness to θ = 27.48°	99.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9895 and 0.9705	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2773 / 0 / 158	
Goodness-of-fit on F^2	0.984	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0306, $wR2$ = 0.1038	
R indices (all data)	$R1$ = 0.0318, $wR2$ = 0.1059	
Absolute structure parameter	0.7(8)	
Extinction coefficient	0.037(11)	
Largest diff. peak and hole	0.222 and –0.165 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	611(2)	2532(1)	1089(1)	17(1)	1
C2	−261(2)	4012(1)	912(1)	18(1)	1
C3	−1612(2)	4444(1)	1433(1)	20(1)	1
C4	−1604(2)	3365(1)	1869(1)	18(1)	1
C5	3014(2)	2607(2)	1187(1)	23(1)	1
C6	−127(2)	1407(1)	606(1)	17(1)	1
C7	685(2)	−100(1)	741(1)	22(1)	1
C8	38(2)	−1153(1)	218(1)	27(1)	1
C9	−2738(2)	3251(1)	2483(1)	18(1)	1
C10	−2255(2)	2146(1)	2913(1)	21(1)	1
C11	−3385(2)	2041(1)	3487(1)	25(1)	1
C12	−4999(2)	3011(1)	3628(1)	26(1)	1
C13	−5477(2)	4115(2)	3202(1)	25(1)	1
C14	−4335(2)	4237(1)	2635(1)	22(1)	1
O1	−377(1)	2230(1)	1711(1)	18(1)	1
O2	210(2)	4647(1)	414(1)	23(1)	1
O3	−2397(1)	1483(1)	609(1)	22(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.4612(14)	C7–H7A	0.9900
C1–C5	1.5178(16)	C7–H7B	0.9900
C1–C6	1.5252(16)	C8–H8A	0.9800
C1–C2	1.5290(17)	C8–H8B	0.9800
C2–O2	1.2285(15)	C8–H8C	0.9800
C2–C3	1.4322(17)	C9–C14	1.3935(18)
C3–C4	1.3555(17)	C9–C10	1.3973(17)
C3–H3	0.9500	C10–C11	1.3923(18)
C4–O1	1.3474(14)	C10–H10	0.9500
C4–C9	1.4645(17)	C11–C12	1.386(2)
C5–H5A	0.9800	C11–H11	0.9500
C5–H5B	0.9800	C12–C13	1.3897(19)
C5–H5C	0.9800	C12–H12	0.9500
C6–O3	1.4208(15)	C13–C14	1.3839(18)
C6–C7	1.5196(16)	C13–H13	0.9500
C6–H6	1.0000	C14–H14	0.9500
C7–C8	1.5203(17)	O3–H3A	0.8400
O1–C1–C5	107.95(10)	C6–C7–H7B	109.2
O1–C1–C6	108.89(9)	C8–C7–H7B	109.2
C5–C1–C6	114.83(10)	H7A–C7–H7B	107.9
O1–C1–C2	103.72(9)	C7–C8–H8A	109.5
C5–C1–C2	110.10(10)	C7–C8–H8B	109.5
C6–C1–C2	110.72(9)	H8A–C8–H8B	109.5
O2–C2–C3	130.09(12)	C7–C8–H8C	109.5
O2–C2–C1	123.56(11)	H8A–C8–H8C	109.5
C3–C2–C1	106.34(10)	H8B–C8–H8C	109.5
C4–C3–C2	107.20(10)	C14–C9–C10	119.69(11)
C4–C3–H3	126.4	C14–C9–C4	119.84(11)
C2–C3–H3	126.4	C10–C9–C4	120.46(11)
O1–C4–C3	114.96(10)	C11–C10–C9	119.49(12)
O1–C4–C9	115.57(10)	C11–C10–H10	120.3
C3–C4–C9	129.47(11)	C9–C10–H10	120.3
C1–C5–H5A	109.5	C12–C11–C10	120.26(12)
C1–C5–H5B	109.5	C12–C11–H11	119.9
H5A–C5–H5B	109.5	C10–C11–H11	119.9
C1–C5–H5C	109.5	C11–C12–C13	120.38(12)
H5A–C5–H5C	109.5	C11–C12–H12	119.8
H5B–C5–H5C	109.5	C13–C12–H12	119.8
O3–C6–C7	112.29(10)	C14–C13–C12	119.54(13)
O3–C6–C1	105.35(9)	C14–C13–H13	120.2
C7–C6–C1	114.37(10)	C12–C13–H13	120.2
O3–C6–H6	108.2	C13–C14–C9	120.62(12)
C7–C6–H6	108.2	C13–C14–H14	119.7
C1–C6–H6	108.2	C9–C14–H14	119.7
C6–C7–C8	112.05(10)	C4–O1–C1	107.77(9)
C6–C7–H7A	109.2	C6–O3–H3A	109.5
C8–C7–H7A	109.2		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	16(1)	20(1)	15(1)	0(1)	1(1)	0(1)
C2	18(1)	18(1)	19(1)	−1(1)	−1(1)	0(1)
C3	21(1)	18(1)	20(1)	−1(1)	2(1)	2(1)
C4	16(1)	19(1)	18(1)	−3(1)	−1(1)	0(1)
C5	17(1)	27(1)	26(1)	−1(1)	−3(1)	0(1)
C6	15(1)	21(1)	16(1)	0(1)	0(1)	1(1)
C7	24(1)	21(1)	21(1)	−2(1)	−2(1)	4(1)
C8	31(1)	22(1)	28(1)	−6(1)	−1(1)	2(1)
C9	18(1)	20(1)	16(1)	−3(1)	−1(1)	−2(1)
C10	25(1)	19(1)	19(1)	−2(1)	0(1)	−1(1)
C11	35(1)	22(1)	18(1)	0(1)	0(1)	−4(1)
C12	30(1)	28(1)	19(1)	−4(1)	6(1)	−8(1)
C13	25(1)	26(1)	23(1)	−5(1)	3(1)	0(1)
C14	24(1)	22(1)	19(1)	−1(1)	1(1)	2(1)
O1	20(1)	18(1)	14(1)	0(1)	1(1)	4(1)
O2	26(1)	22(1)	22(1)	3(1)	5(1)	2(1)
O3	16(1)	26(1)	23(1)	−5(1)	−2(1)	3(1)